

Epigenetics

EPIGENETICS IN CANCER CONTROL AND PREVENTION: ARE WE READY FOR THE PRIME TIME?



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Epigenetics

Epigenetics:

Stable alterations in gene expression by several mechanisms, except nucleotide sequence changes

Genetic Code

The two main components of the epigenetic code

DNA methylation

Methyl marks added to certain DNA bases repress gene activity.

Methylation Code

Histone Code

Histone modification

A combination of different molecules can attach to the 'tails' of proteins called histones. These

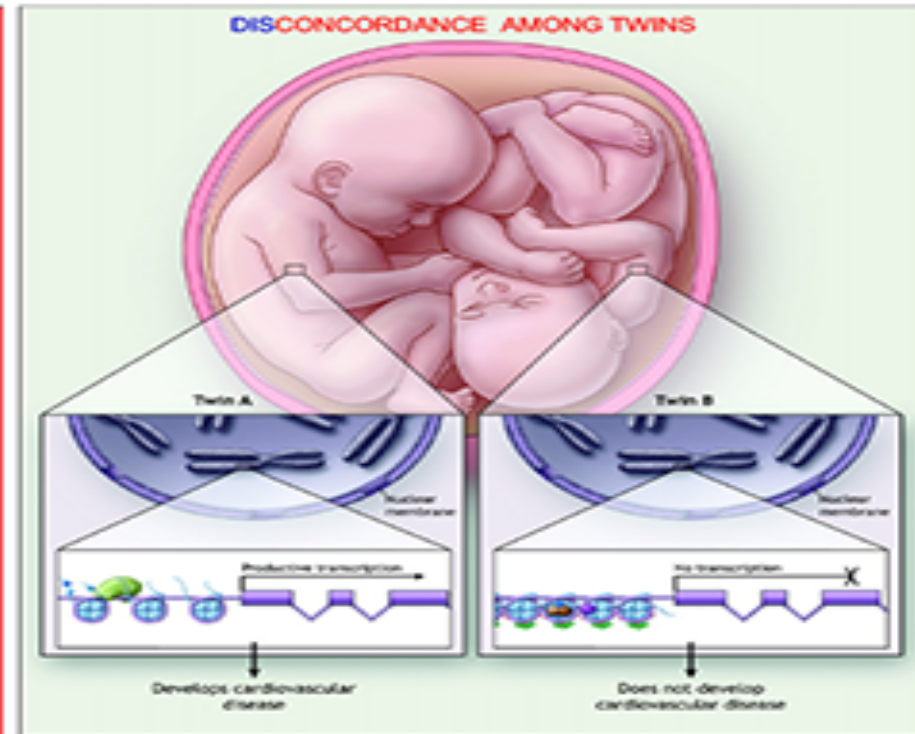
The genetic information provides the blue print for the manufacture of all the proteins necessary to create a living organism, whereas the epigenetic information provides the instructions on how, where and when the genetic information will be used.



DNA and destiny



The choices you make
can change your genes
— and those of your kids.



Epigenetic predisposition to angiogenesis? Individual? Populations?

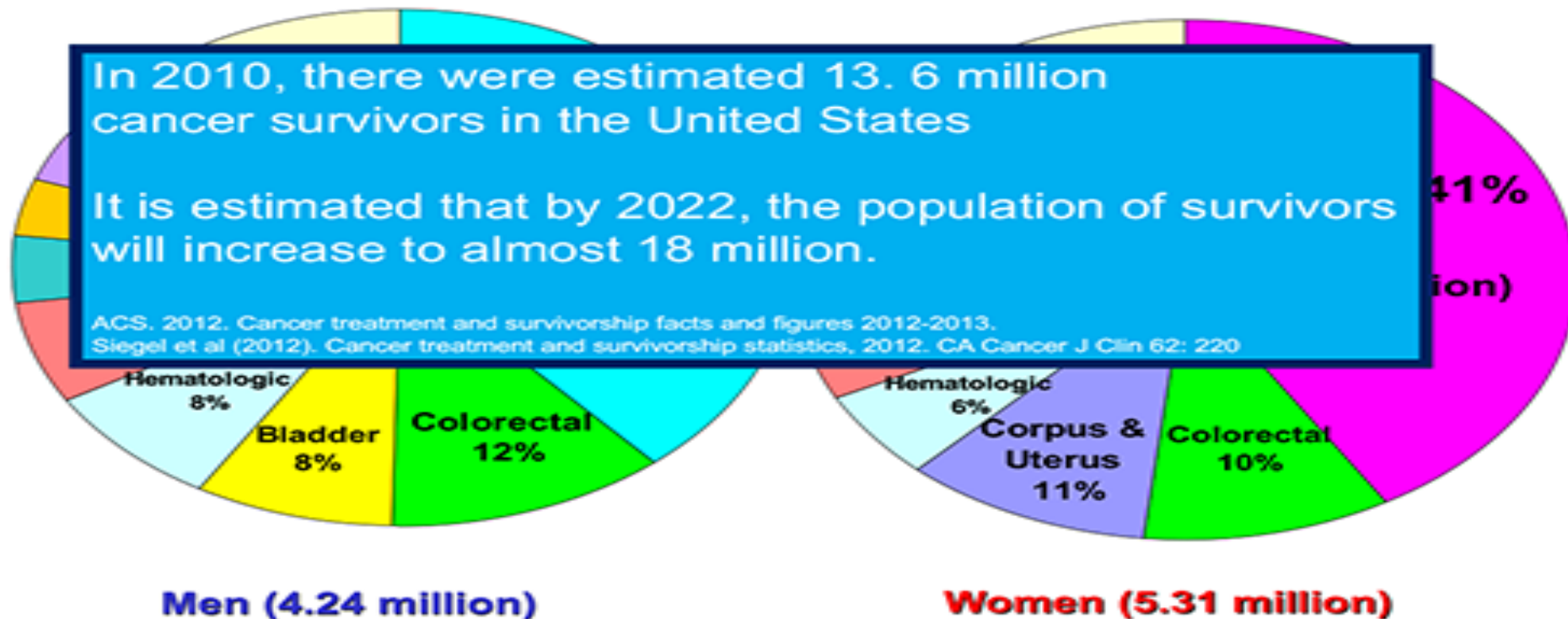
Pharmacogenomics and pharmacoepigonomics (personalized medicine)

Microenvironment, microbiome, and gene expression

GWAS and EWAS

Cancer Survivors

Estimated Number of Persons Alive in the U.S. Diagnosed with Cancer by Site



Cancer continuum

DCCPS covers cancer continuum



Prevention

Tobacco, physical activity, diet, sun, environment, HPV immunization



Early Detection

Breast, cervical, colorectal cancer screening



Diagnosis

Incidence, Stage at diagnosis



Treatment

Trends in cancer treatment



Life After Cancer

Financial burden of cancer care, Cancer survivorship



End of Life

Mortality, Person – years of life lost

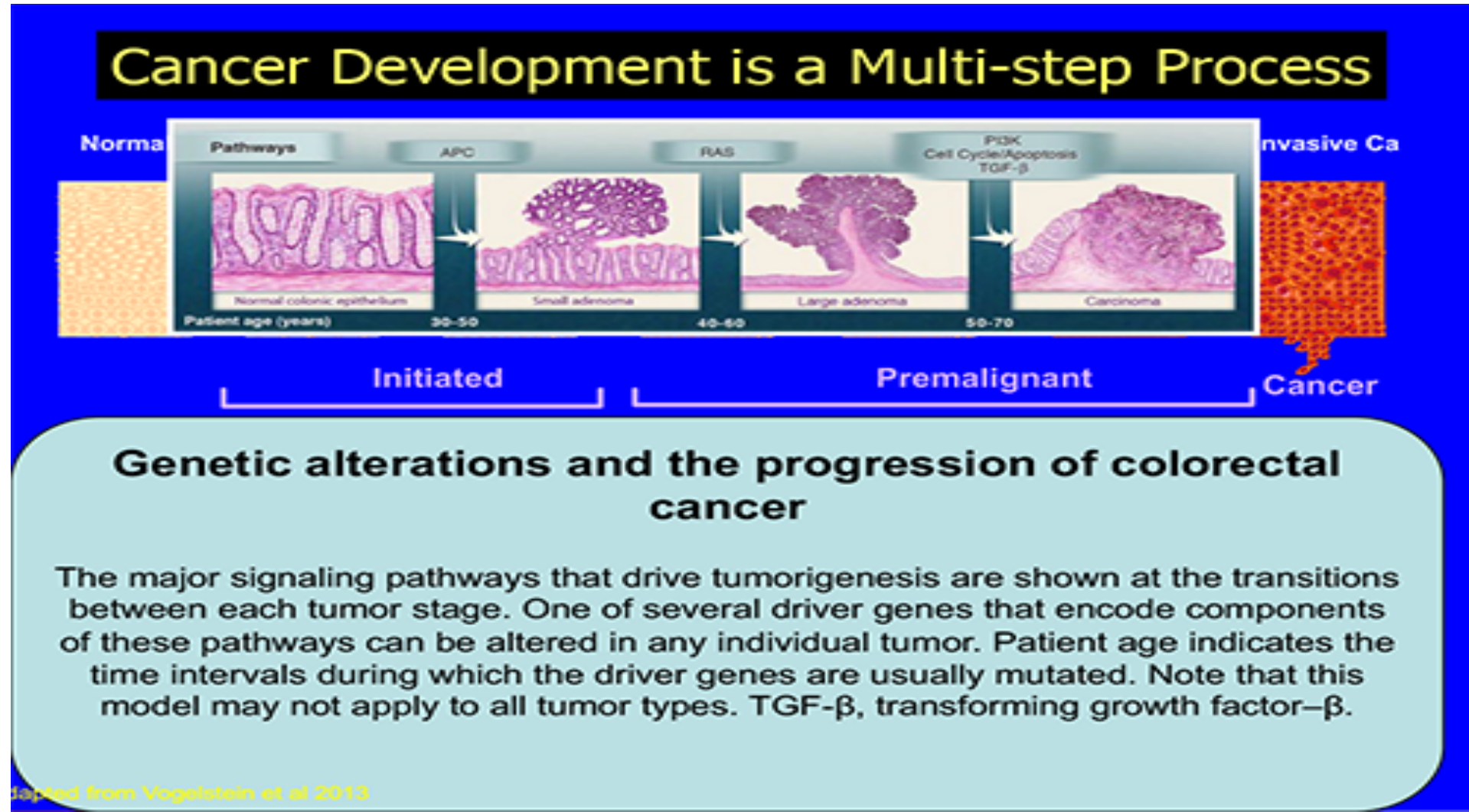
Prevention



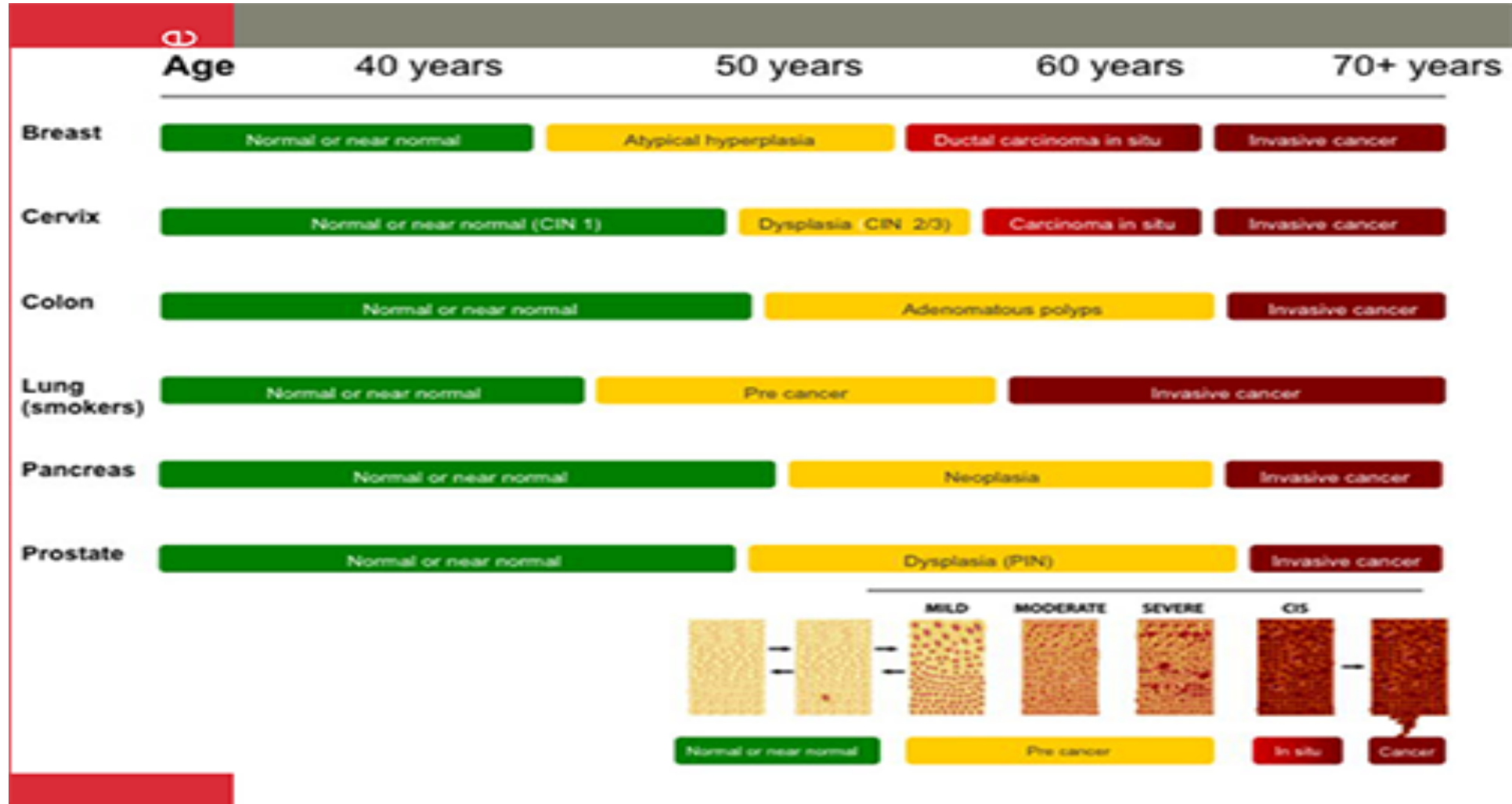
Cancer recurrence
Secondary cancer

Prevention: restoring transcription,
halting progression, or stopping
metastasis

Cancer development



Cancer and age

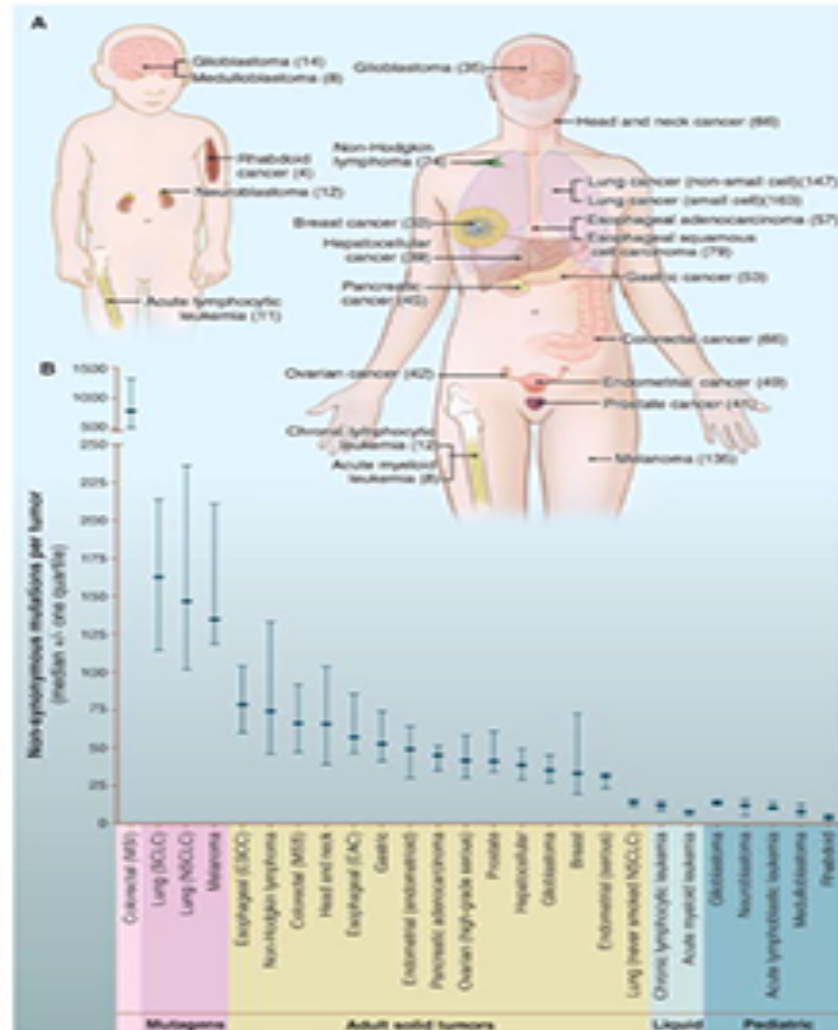


Paradigm shift

Paradigm shifts in genetics

1850 -1900 : Proto-genetics	<i>Mendelian inheritance Darwin, natural selection</i>
1900 -1950 : Age of genetics	<i>gene concept, mutation, genotype-phenotype</i>
1950-2000 : Age of DNA	<i>structure, genetic code, genome sequence</i>
2000 - : Age of epigenetics	<i>epigenetic code, epigenome, epigenetic medicine</i>

Genome landscape



CANCER GENOME LANDSCAPE
 Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies



Adapted from Vogelstein and Kinzler (Science 2013)

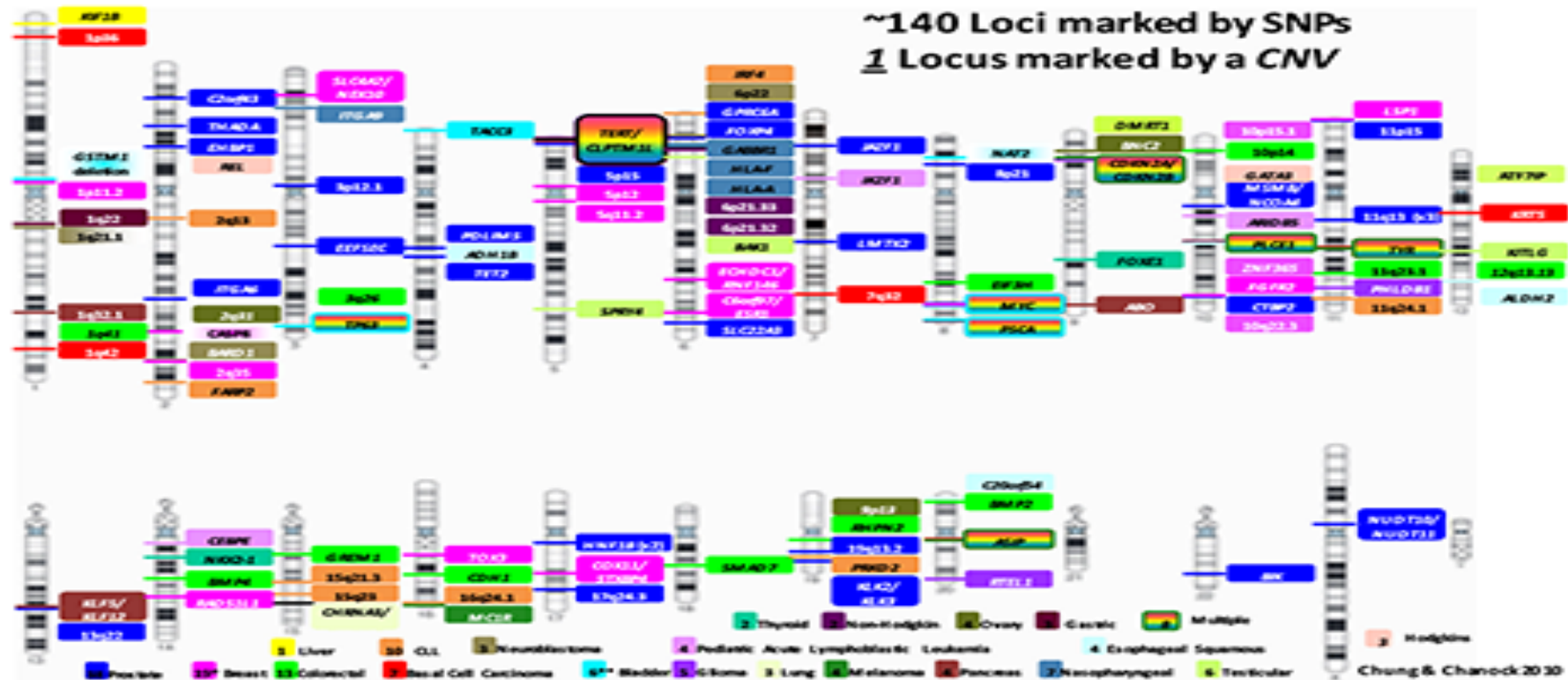
Cancer genes



Adapted from T. Manolio

GWAS hits

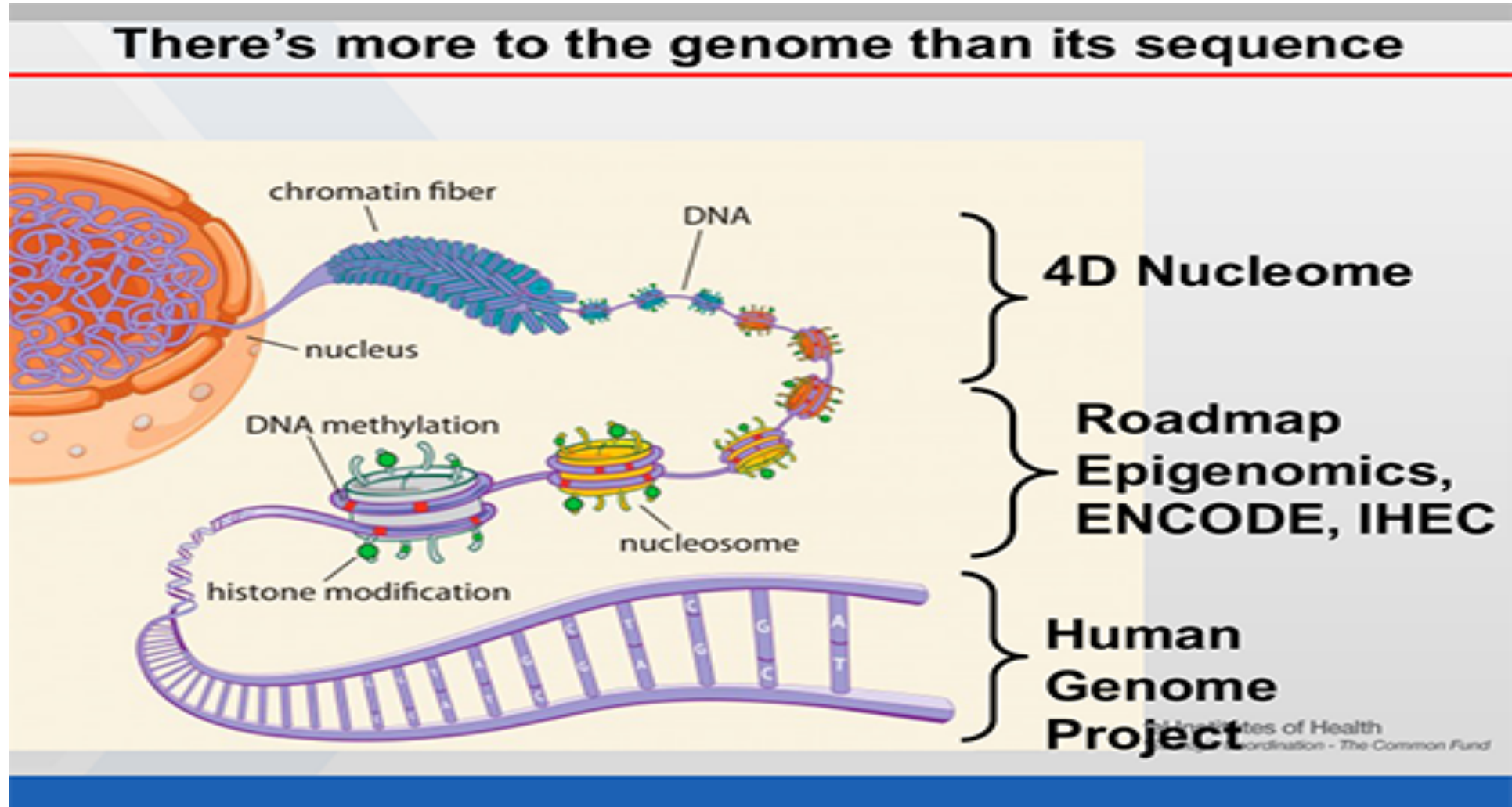
Published GWAS Etiology Hits (2010)



Genome wide associations



Genome sequence



Kornberg and nucleosome

Nucleosomes (Units of Chromatin)

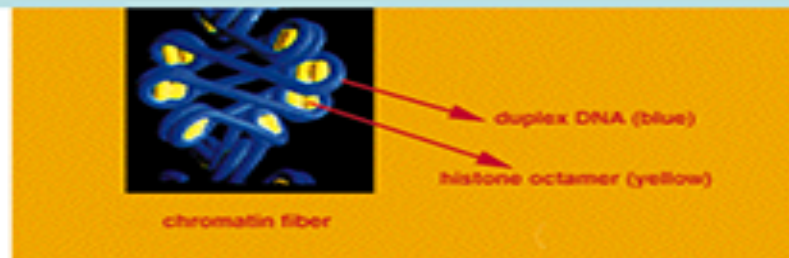
DNA
Histones H2a, H2b, H3, H4

To neutralize charge and provide stability

H1 is a linker histone which binds to the DNA linking two adjacent nucleosomal cores

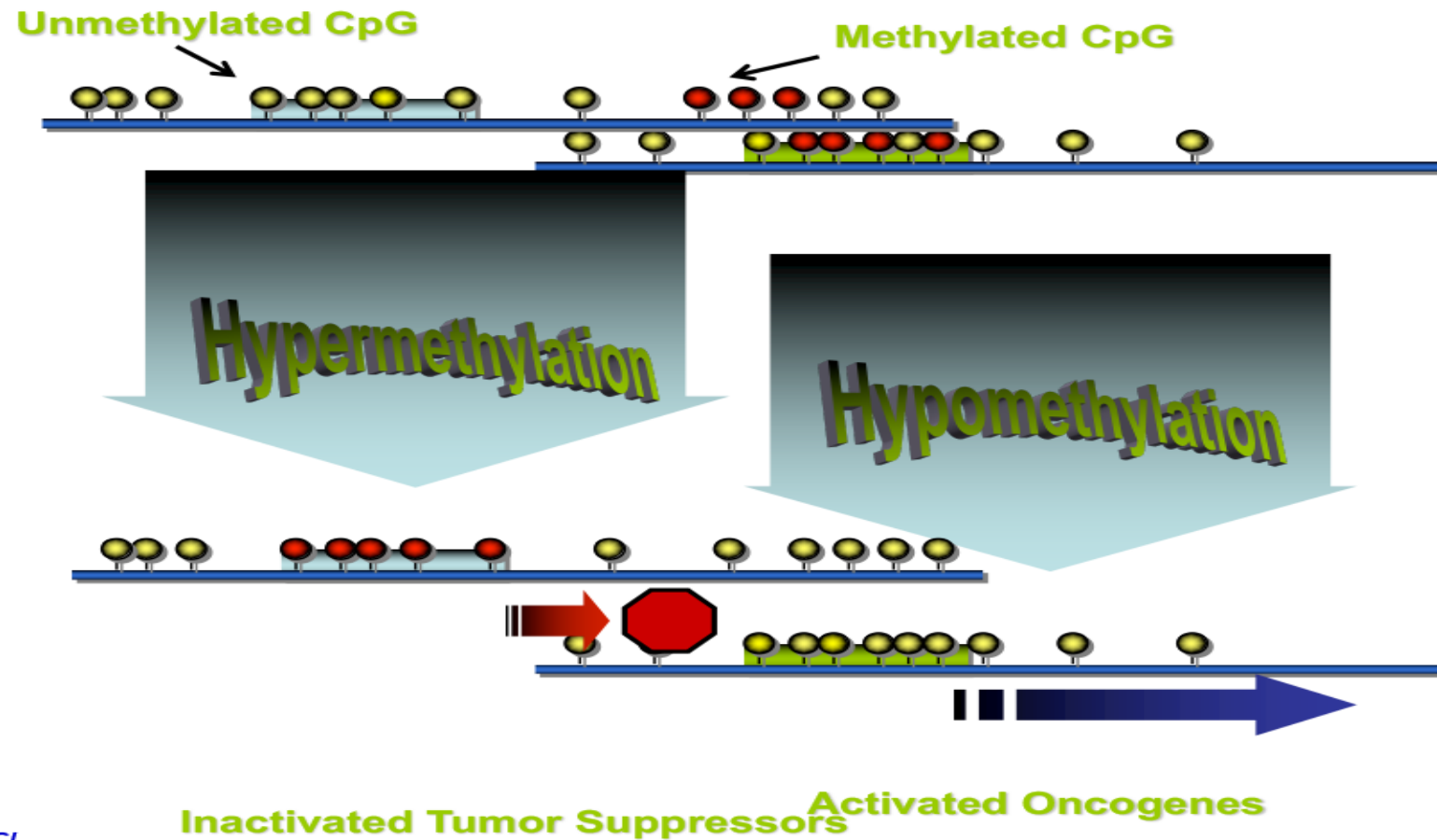
Nucleosome: two turns of DNA (146 base pairs) wrapped around an octomeric complex of two of each of histone types

1974: Roger Kornberg discovers nucleosome who won Nobel Prize in 2006.



Shores are 0-2kb from islands
Shelves are 2-4 kb and enhancers are beyond shelves

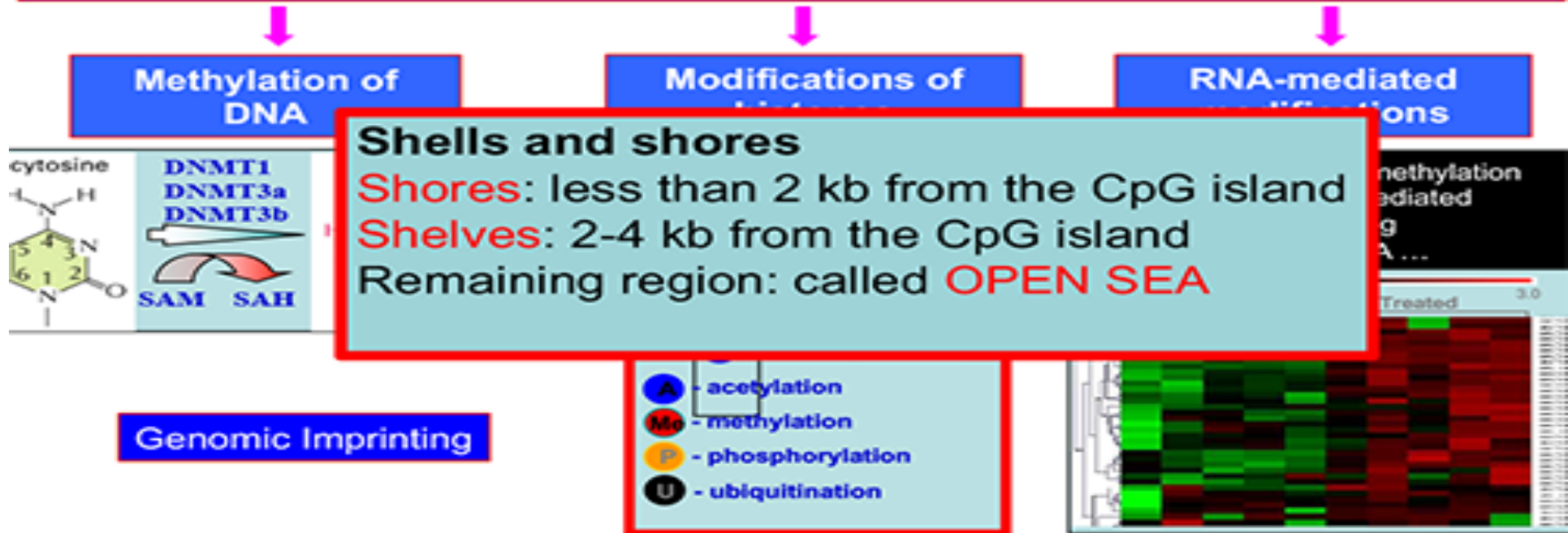
DNA methylation



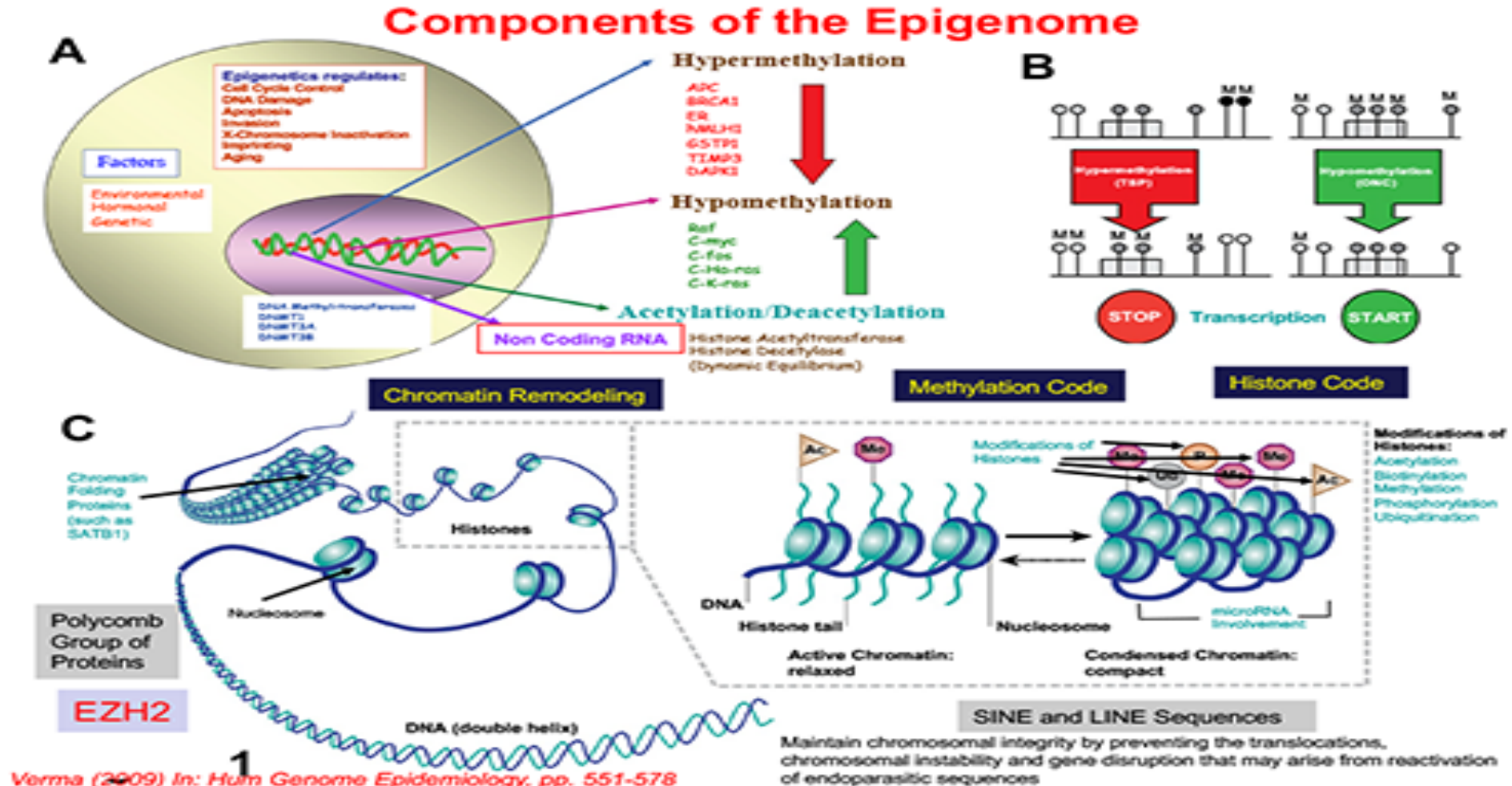
Epigenetics

EPIGENETICS

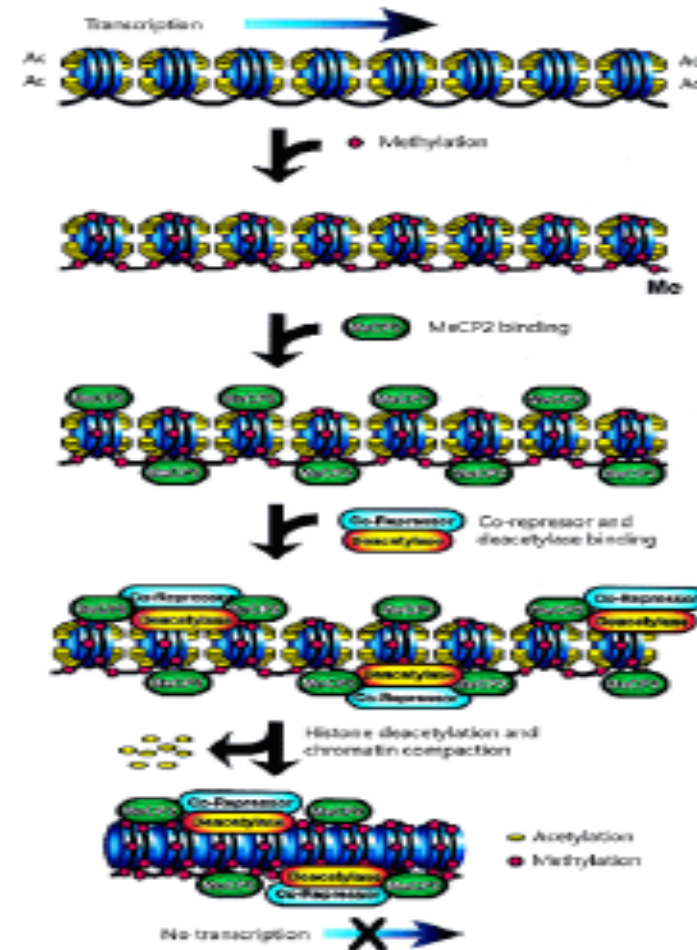
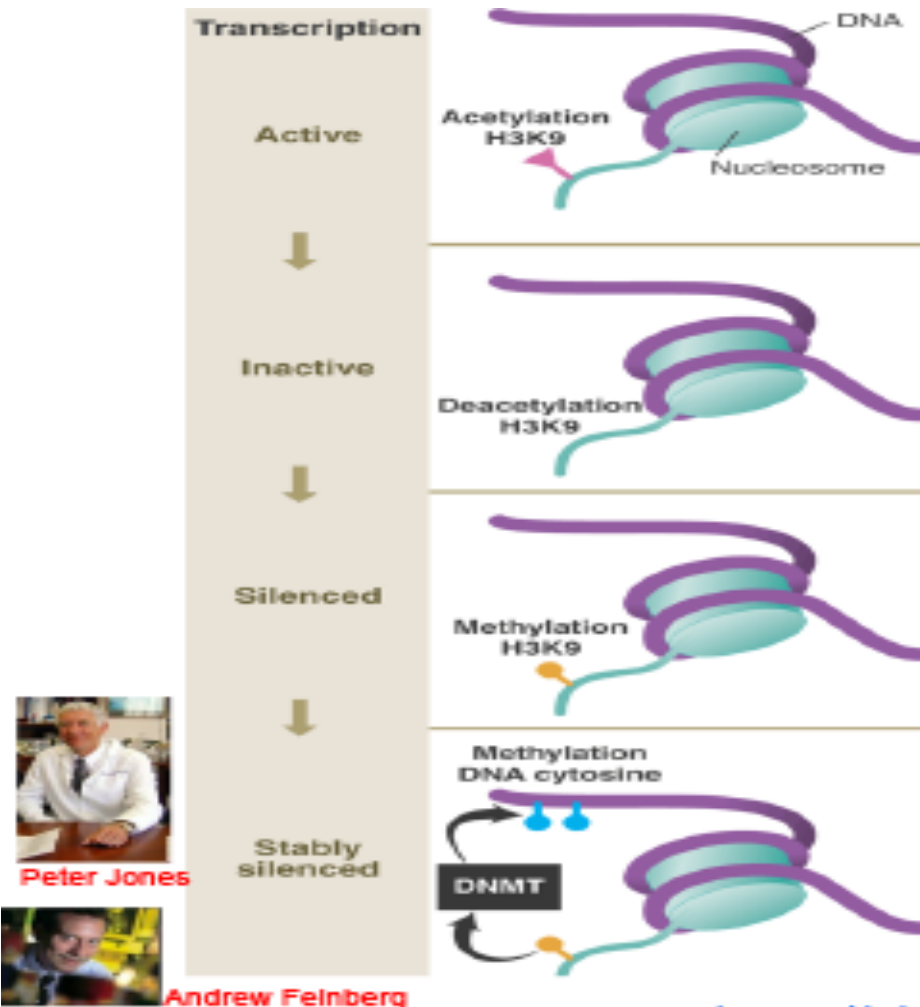
Epigenetic alterations – changes induced in cells that alter expression of the information on transcriptional, translational, or post-translational levels without change in DNA sequence



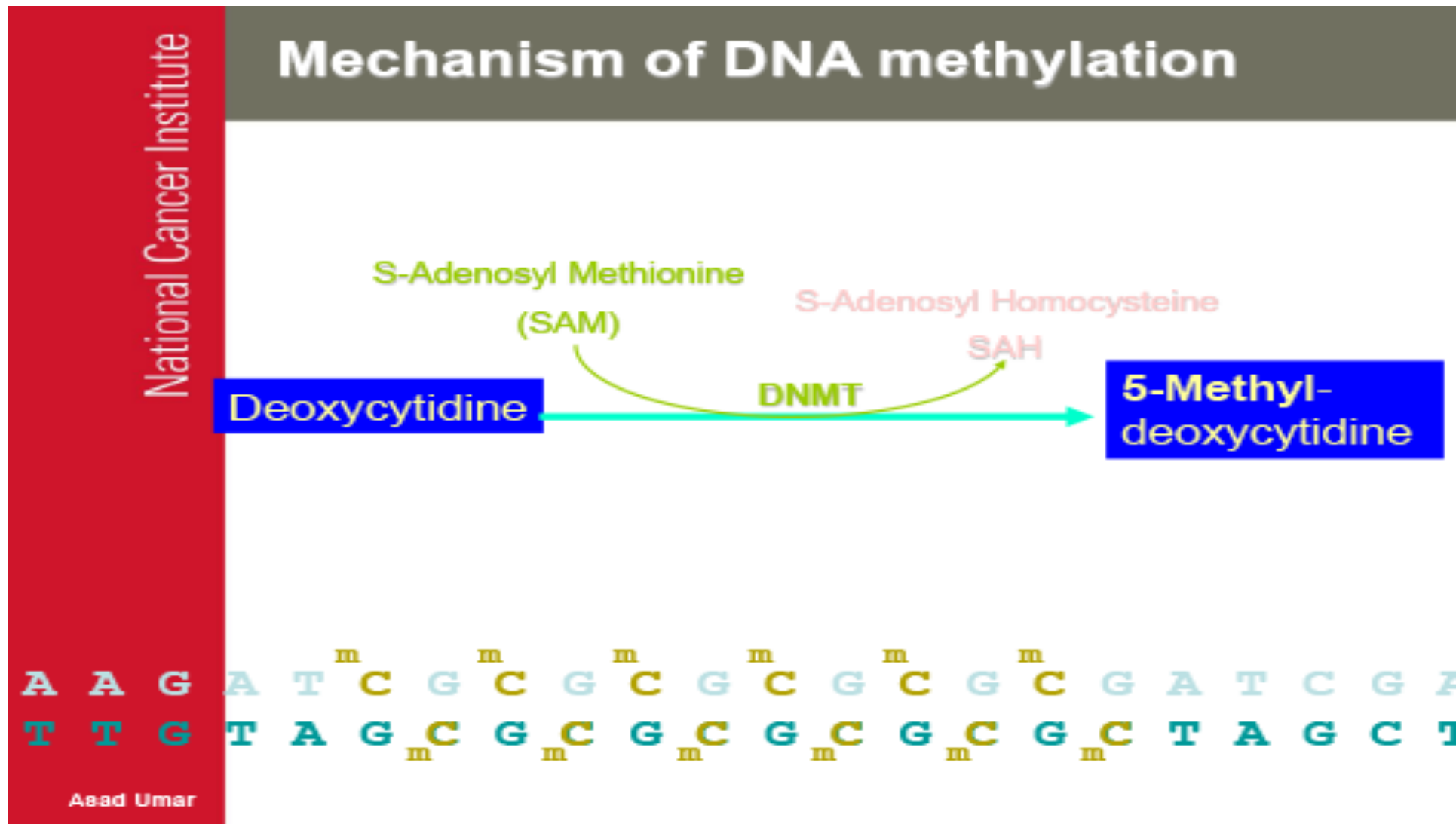
Epigenome components



Methylation



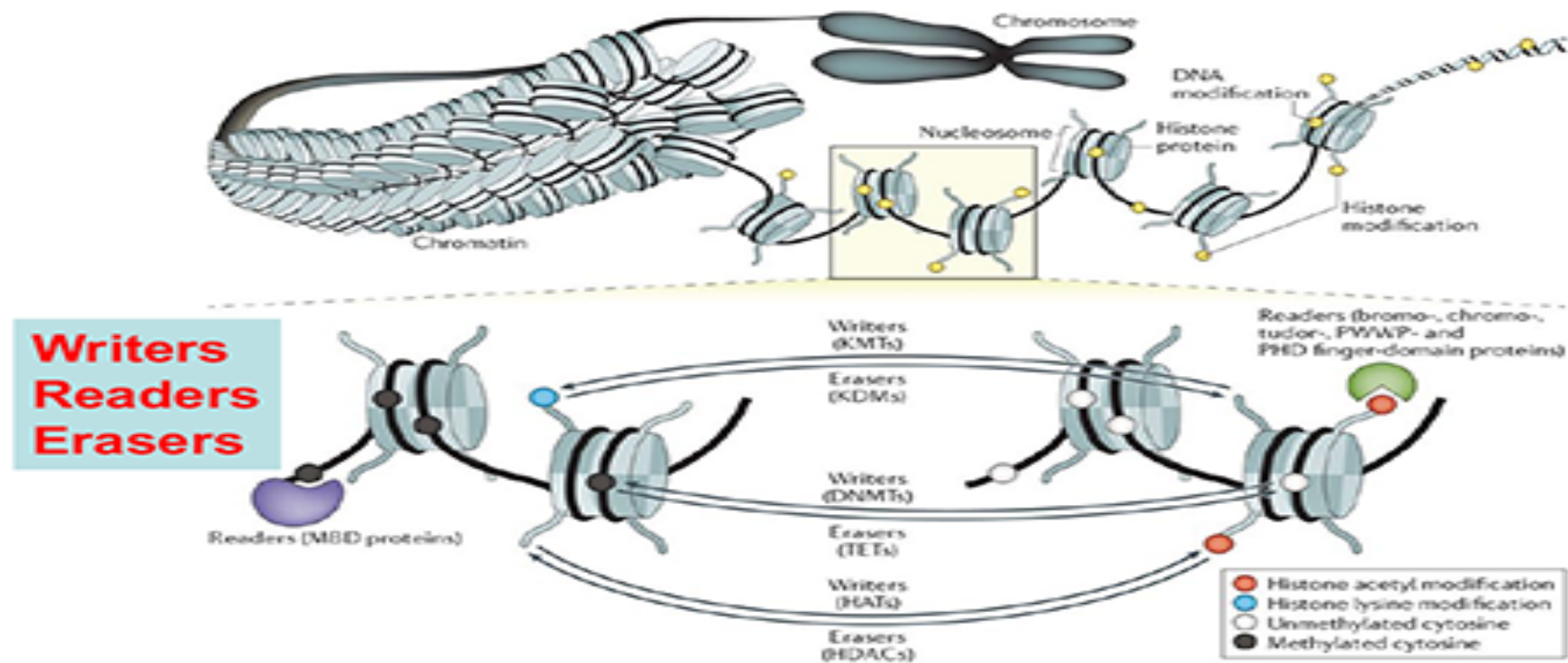
Mechanism



Chromatin modifications

Figure 1 : Modulation of covalent modifications on chromatin.

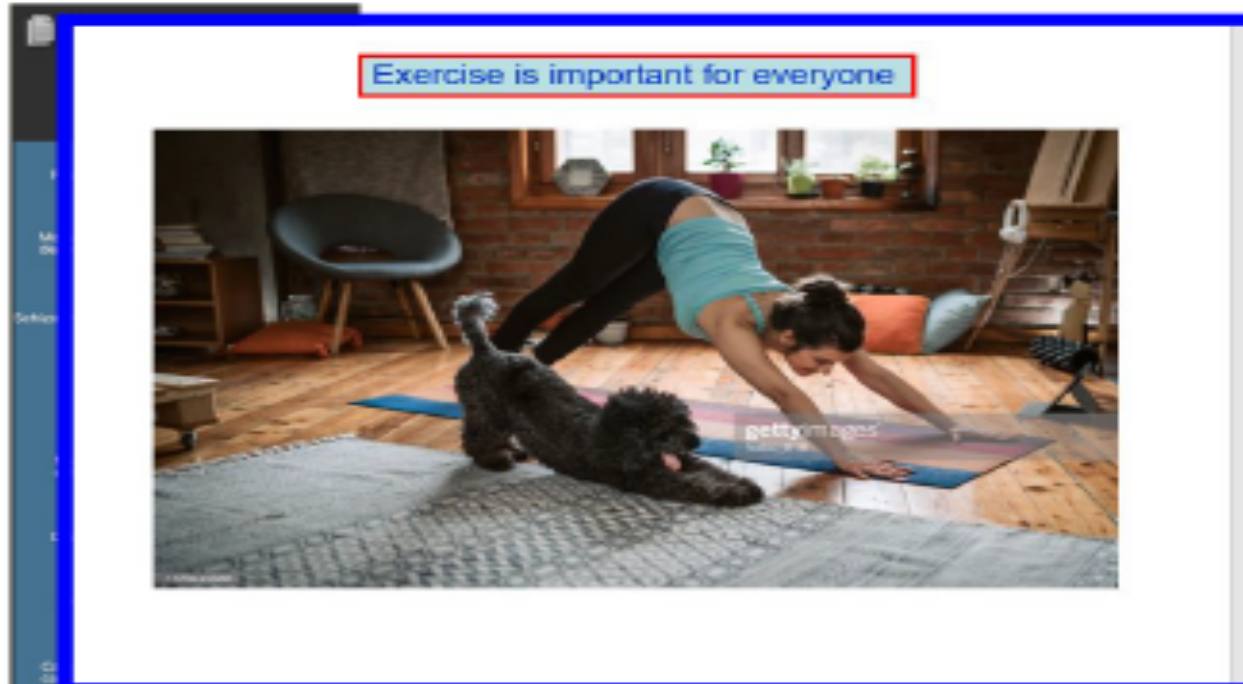
From: Targeting the cancer epigenome for therapy



Ten-eleven translocation (TET) family of 5-methylcytosine oxidases.

Nature Reviews | Genetics

Exercise



important?



changes

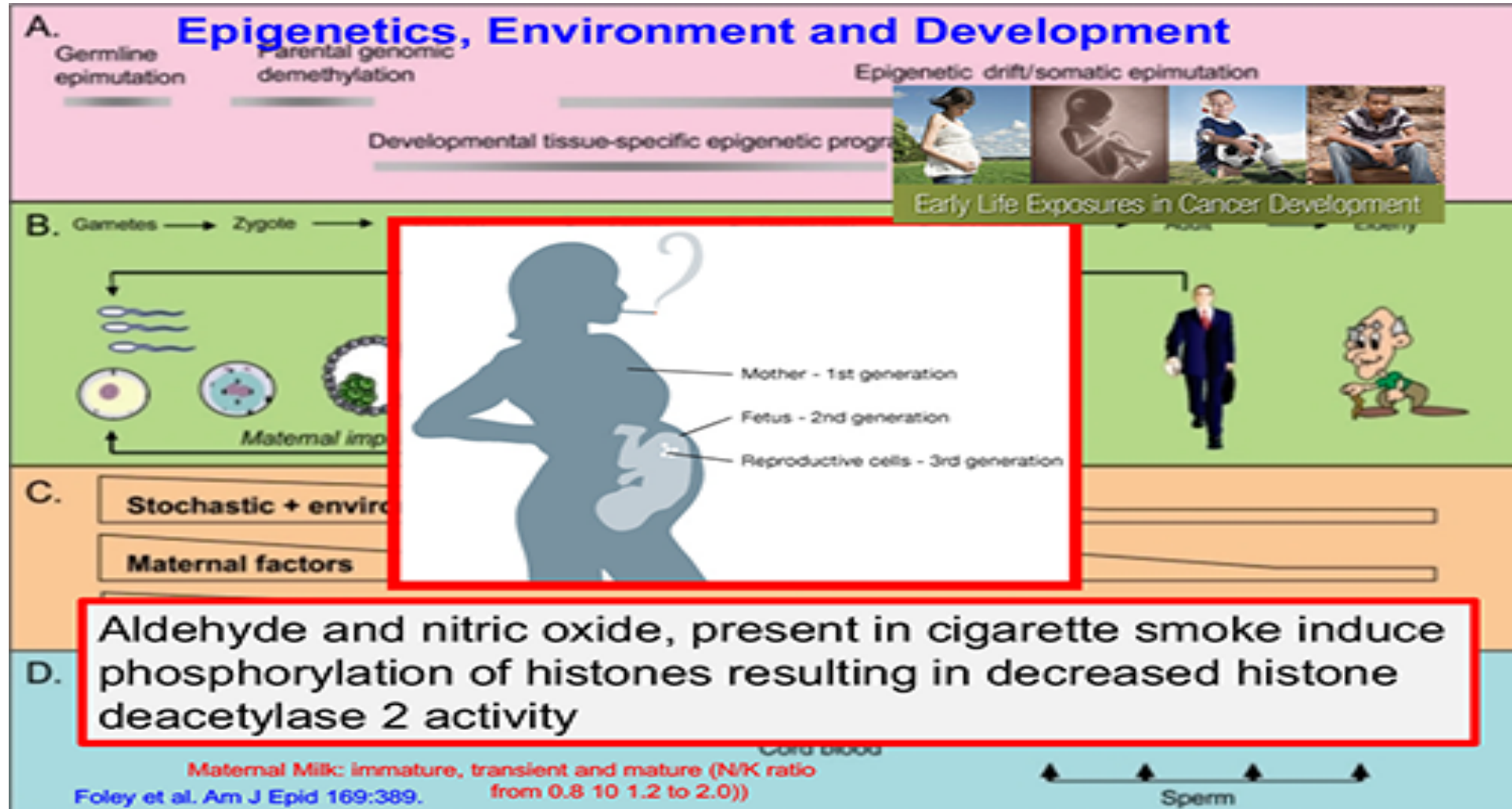


- Drug targeting

**You only need to sequence your genome once,
but you need to determine your epigenome
multiple times...**

<https://www.youtube.com/watch?v=JMT6oRYgkTk>

Environment and development



E-cigarette vapors

Vaping can damage
vital immune system



OPEN ACCESS

ORIGINAL ARTICLE

Pro-inflammatory effects of e-cigarette vapour condensate on human alveolar macrophages

Aaron Scott,¹ Sebastian T Lugg,¹ Kerrie Aldridge,¹ Keir E Lewis,² Allen Bowden,³ Rahul Y Mahida,¹ Frances Susanna Grudzinska,¹ Davinder Dosanjh,¹ Dhruv Parekh,¹ Robert Foronjy,⁴ Elizabeth Sapey,¹ Babu Naidu,¹ David R Thickett¹

ABSTRACT

Objective: Vaping may increase the cytotoxic effects of e-cigarette liquid (ECL). We compared the effect of unspiced ECL to e-cigarette vapour condensate (ECVC) on alveolar macrophage (AM) function.

Methods: AMs were treated with ECVC and nicotine-free ECVC (nECVC). AM viability, apoptosis, necrosis, cytokine, chemokine and protease release, reactive oxygen species (ROS) release and bacterial phagocytosis were assessed.

Key messages

What is the key question?

► Do e-cigarettes have a negative impact on alveolar macrophage viability and function?

What is the bottom line?

► Vapourised e-cigarette fluid is cytotoxic, pro-inflammatory and inhibits phagocytosis in alveolar macrophages.

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2018-211663>).

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²College of Medicine, Swansea University, Swansea, UK;
³Department of Respiratory, EPR

Thorax first published as 10.1136/thoraxjnl-2018-211663 on

Cancer etiology

Understanding Cancer Etiology and Risk Assessment

Need healthy population (pathologically disease free) (cohort) with information about

- Exposure (Chemicals, Radiations, Infectious Agents, Toxic substance)
- Family History
- Diet and Life Style
- Medication

Need easily collected biospecimens (non-invasive technologies) and analytic tools

Need follow up (for longitudinal studies) for several years

Challenge: Expensive, data sharing

Advantage: Essential to identify risk factors for cancer

EGRP studies

2
9

EGRP Studies Are Everywhere

- Senegal
- Malawi
- The Zambia
- China
- Japan
- Egypt
- Israel
- Brazil
- Colombia
- England
- Canada
- Sweden
- Denmark
- France
- Costa Rica
- Singapore
- Poland
- Australia
- U.S., including Alaska & Hawaii

2.3 Million Subjects

Cohorts, CGN and Family Registries

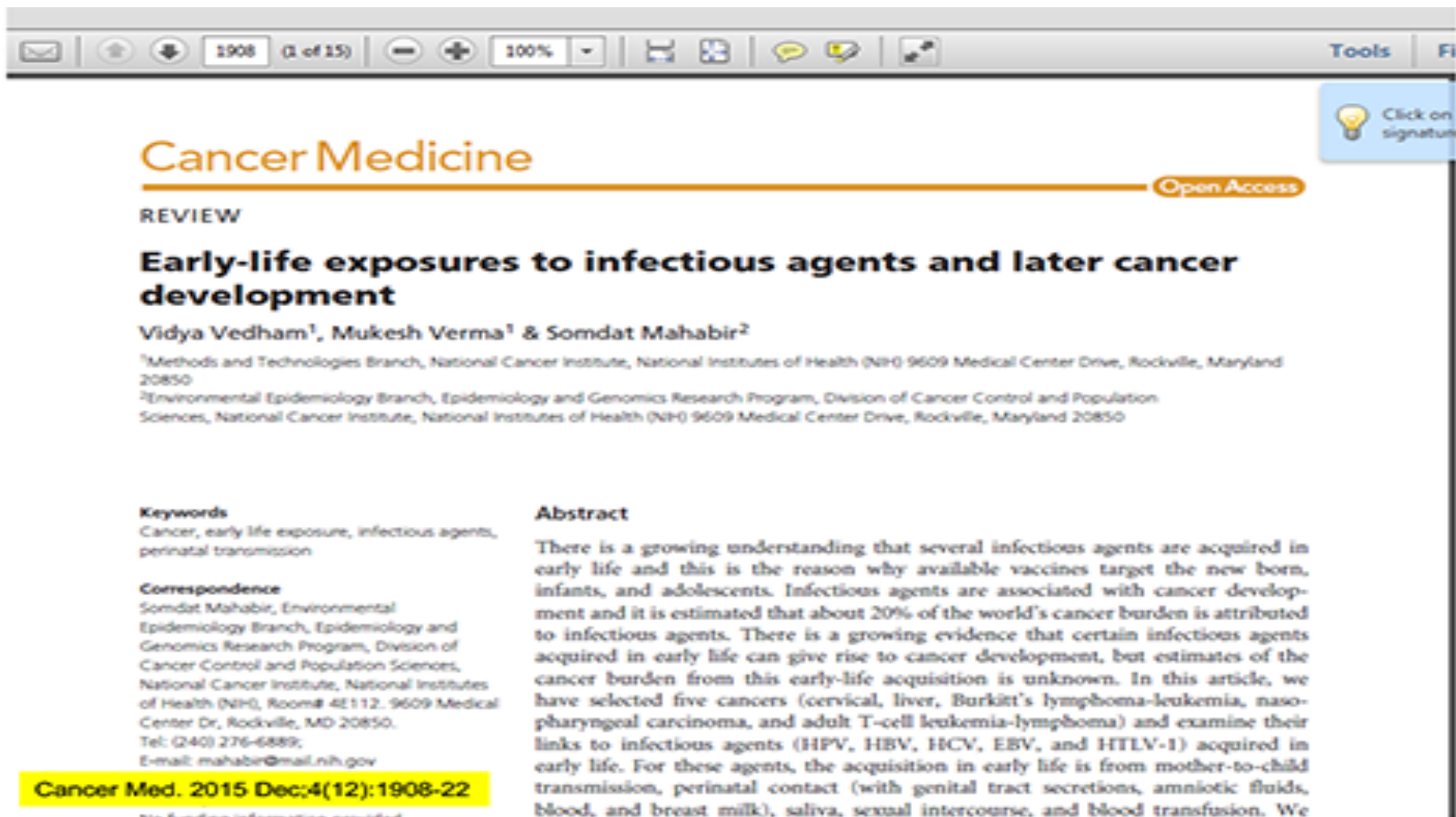
Cohort consortium

The Cohort Consortium (CoCo)



- 62 cohorts, over 4 million individuals
- **Membership**: cohort studies worldwide with >10,000 subjects, blood samples and questionnaire data on important cancer risk factors
- The Cohort Consortium was formed by NCI to address the need for large-scale collaborations for
 - Rapid identification and confirmation of **common polymorphisms** and **cancer susceptibility** (GWAS)
 - Studies of **GxG** and **GxE** interactions in the etiology of cancer.

Early life exposure



The image is a screenshot of a PDF document viewer. At the top, there is a toolbar with various icons for navigation and viewing, including a search icon, a home icon, a download icon, a page number indicator (1908 of 15), a zoom in/out icon, a zoom level dropdown (100%), a print icon, a full screen icon, a comment icon, a signature icon, and a share icon. On the right side of the toolbar, there are links for 'Tools' and 'Full Screen'. Below the toolbar, the document content is displayed. The title 'Cancer Medicine' is in a large, bold, orange font. To the right of the title, there is a blue button with a lightbulb icon and the text 'Click on signature'. Below the title, there is a red 'Open Access' badge. The article is a 'REVIEW' titled 'Early-life exposures to infectious agents and later cancer development' by Vidya Vedham¹, Mukesh Verma¹ & Somdat Mahabir². The authors' affiliations are listed below the title. The 'Keywords' section includes 'Cancer, early life exposure, infectious agents, perinatal transmission'. The 'Correspondence' section provides contact information for Somdat Mahabir. The 'Abstract' section begins with 'There is a growing understanding that several infectious agents are acquired in early life and this is the reason why available vaccines target the new born, infants, and adolescents. Infectious agents are associated with cancer development and it is estimated that about 20% of the world's cancer burden is attributed to infectious agents. There is a growing evidence that certain infectious agents acquired in early life can give rise to cancer development, but estimates of the cancer burden from this early-life acquisition is unknown. In this article, we have selected five cancers (cervical, liver, Burkitt's lymphoma-leukemia, nasopharyngeal carcinoma, and adult T-cell leukemia-lymphoma) and examine their links to infectious agents (HPV, HBV, HCV, EBV, and HTLV-1) acquired in early life. For these agents, the acquisition in early life is from mother-to-child transmission, perinatal contact (with genital tract secretions, amniotic fluids, blood, and breast milk), saliva, sexual intercourse, and blood transfusion. We

Cancer Med. 2015 Dec;4(12):1908-22

See frontmatter information provided

Scientific goal

ECHO Scientific Goal

Answer crucial questions about the effects of a **broad** range of **early environmental influences** on child health and development.



<https://www.nih.gov/echo/pediatric-cohorts>

From
society
to
biology



Health outcomes throughout
childhood and adolescence

ECHO advantages

Developmental Life Stages

Advantages of ECHO Research Design

- Longitudinal cohorts – opportunity to examine repeated measures
 - in utero
 - early in life
 - other transition periods
- Look across multiple tissues in same person
- Unifying/harmonizing epigenetic data with other data (including other omics data)
- Potential for single cell analysis
- Across generation

Adolescence

12 years through 18 (or 21?) years

Placenta, cord blood, nail, hair, saliva, urine
Maternal blood, milk before and after pregnancy

Epigenetics and behavior

Epigenetics and
behavior (including
emotions)



[Transl Psychiatry](#), 2016 Mar 29;6:e765, doi: 10.1038/tp.2016.32.

The effects of maternal anxiety during pregnancy on IGF2/H19 methylation in cord blood.

[Mansell T](#)^{1,2}, [Novakovic B](#)^{1,2}, [Meyer B](#)^{1,2}, [Rzehak P](#)^{1,3}, [Vuillermin P](#)^{1,2,4,5}, [Ponsonby AL](#)^{1,2}, [Collier F](#)^{4,5}, [Burgner D](#)^{1,2}, [Saffery R](#)^{1,2}, [Ryan J](#)^{1,2,6,7}; [BIS investigator team](#).

✚ Collaborators (11)

✚ Author information

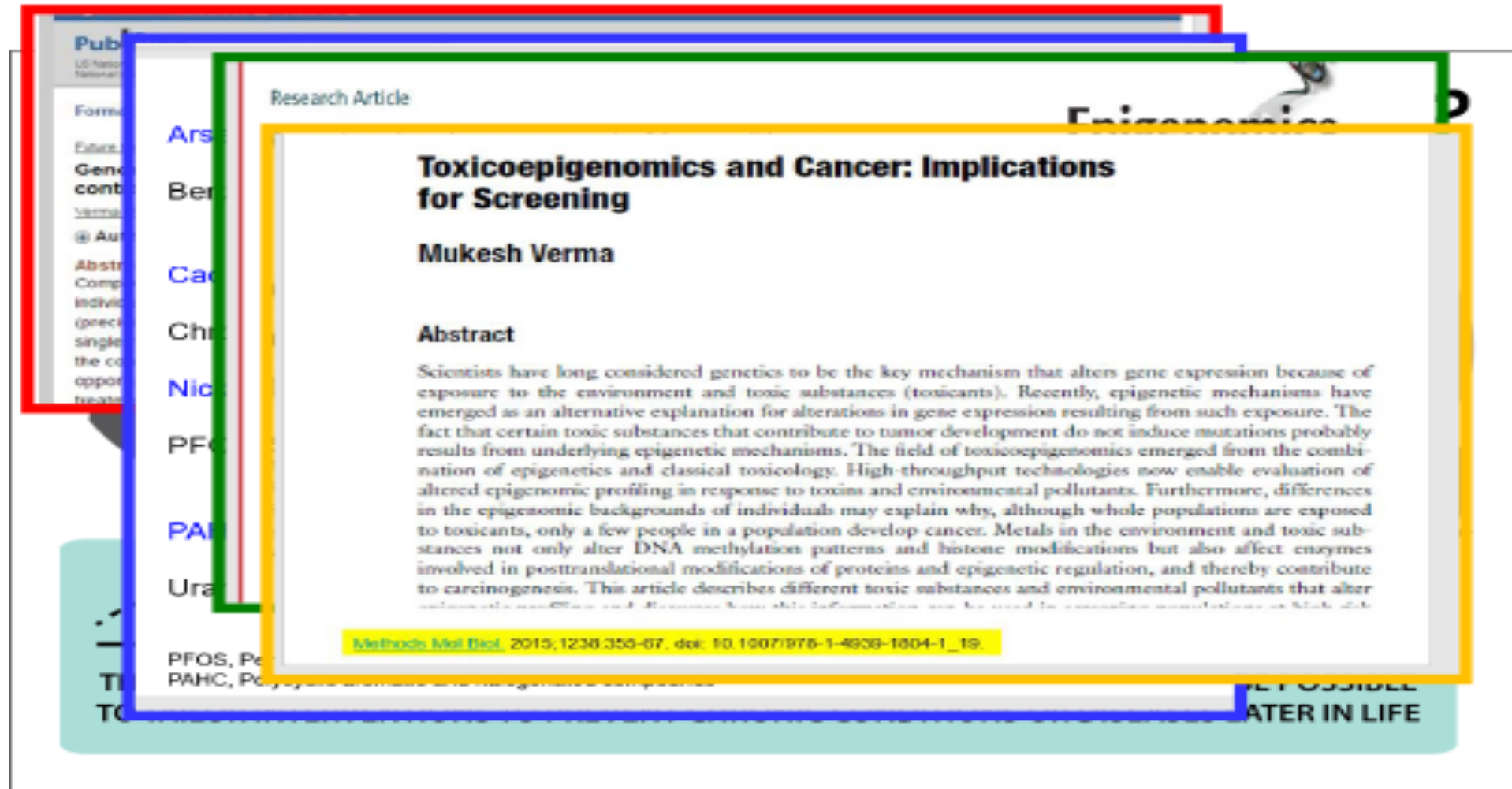
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Abstract

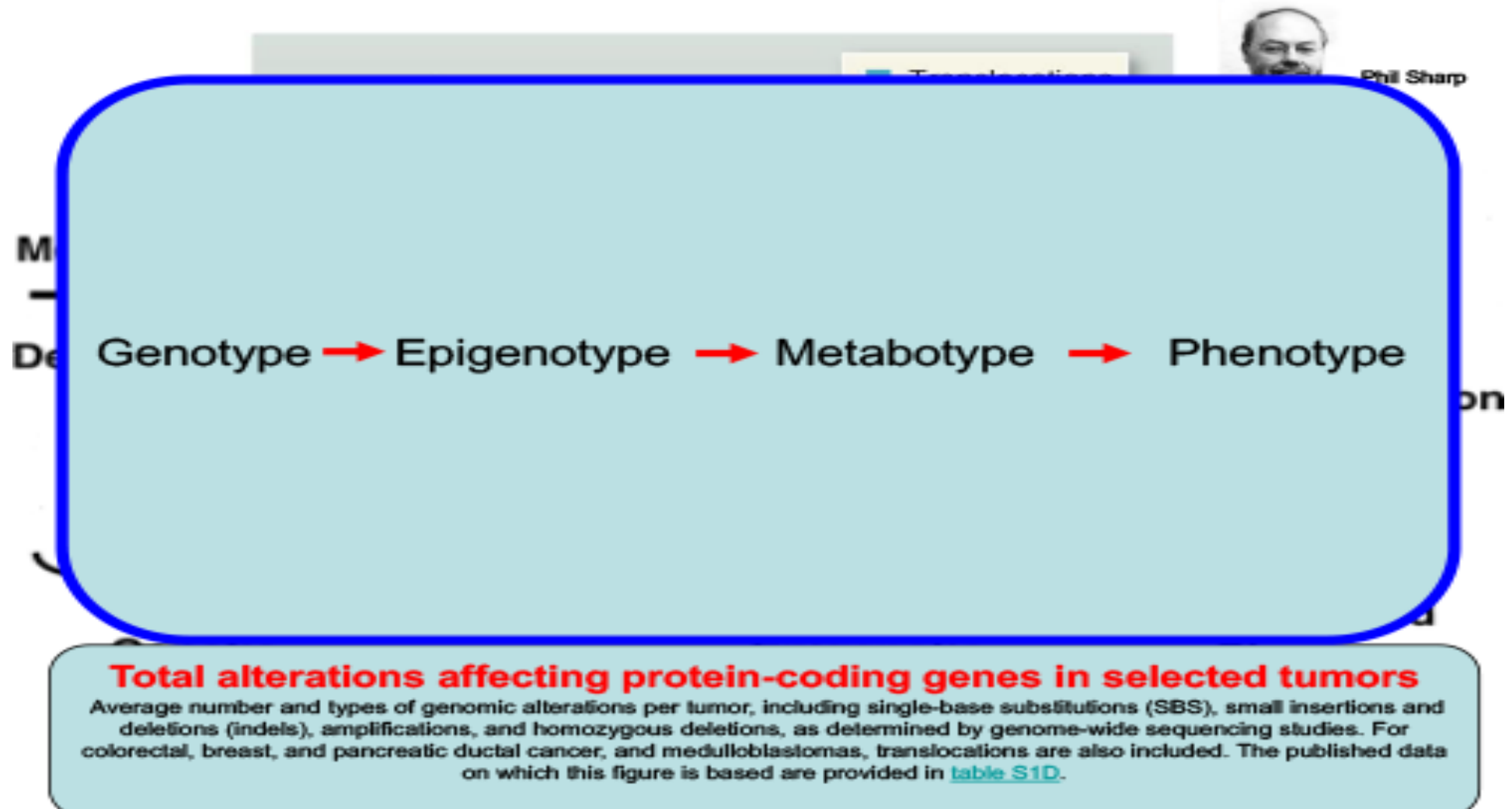
Compelling evidence suggests that maternal mental health in pregnancy can influence fetal development. The imprinted genes, insulin-like growth factor 2 (IGF2) and H19, are involved in fetal growth and each is regulated by DNA methylation. This study aimed to determine the association between maternal mental well-being during pregnancy and differentially methylated regions (DMRs) of IGF2 (DMR0) and the IGF2/H19 imprinting control region (ICR) in newborn offspring. Maternal depression, anxiety and perceived stress were assessed at 28 weeks of pregnancy in the Barwon Infant Study (n=576). DNA methylation was measured in purified cord blood mononuclear cells using the Sequenom

within your DNA that can be controlled by you, by your emotions, beliefs and behavioral choices."

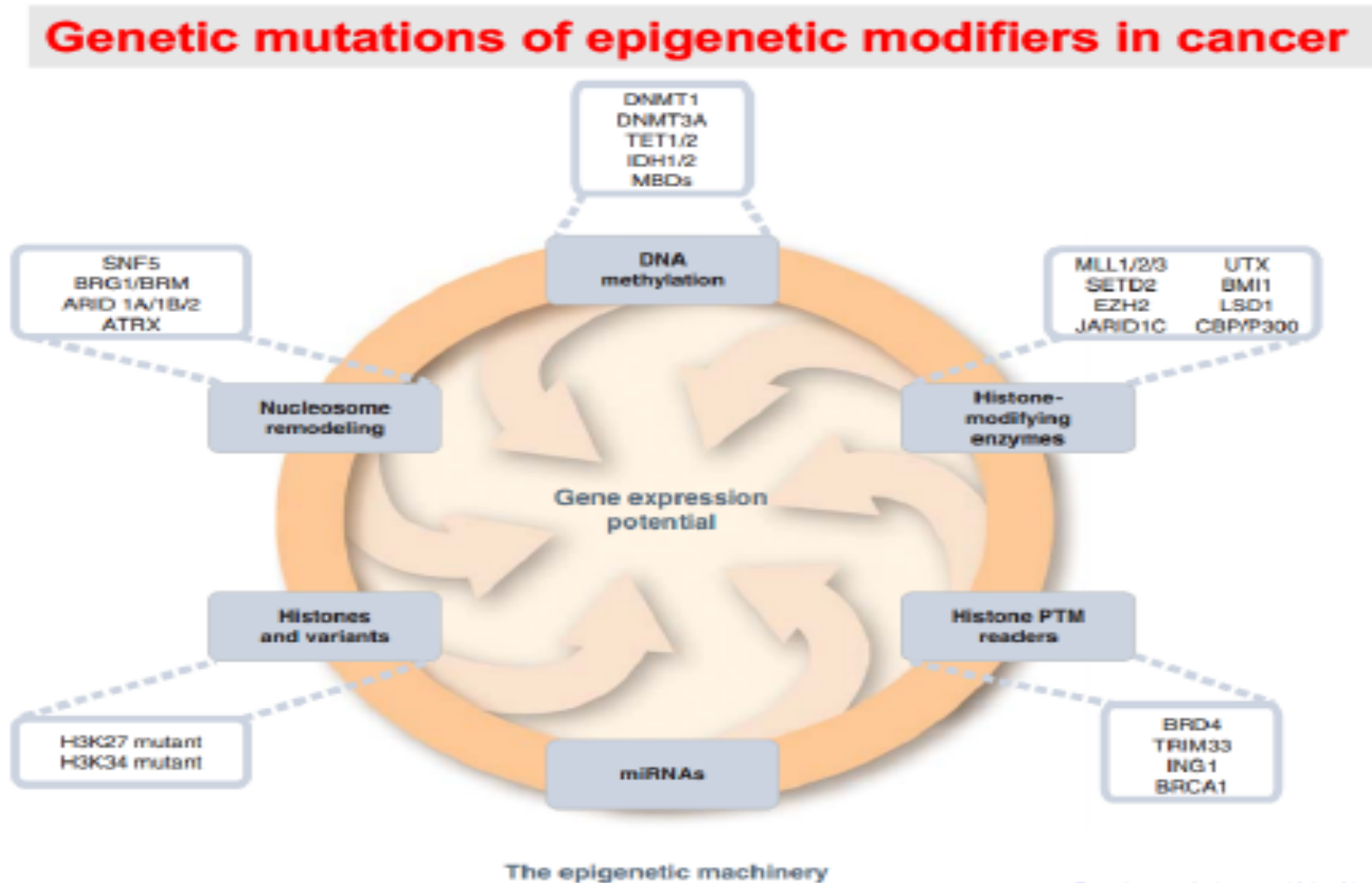
Toxicoepigenomics



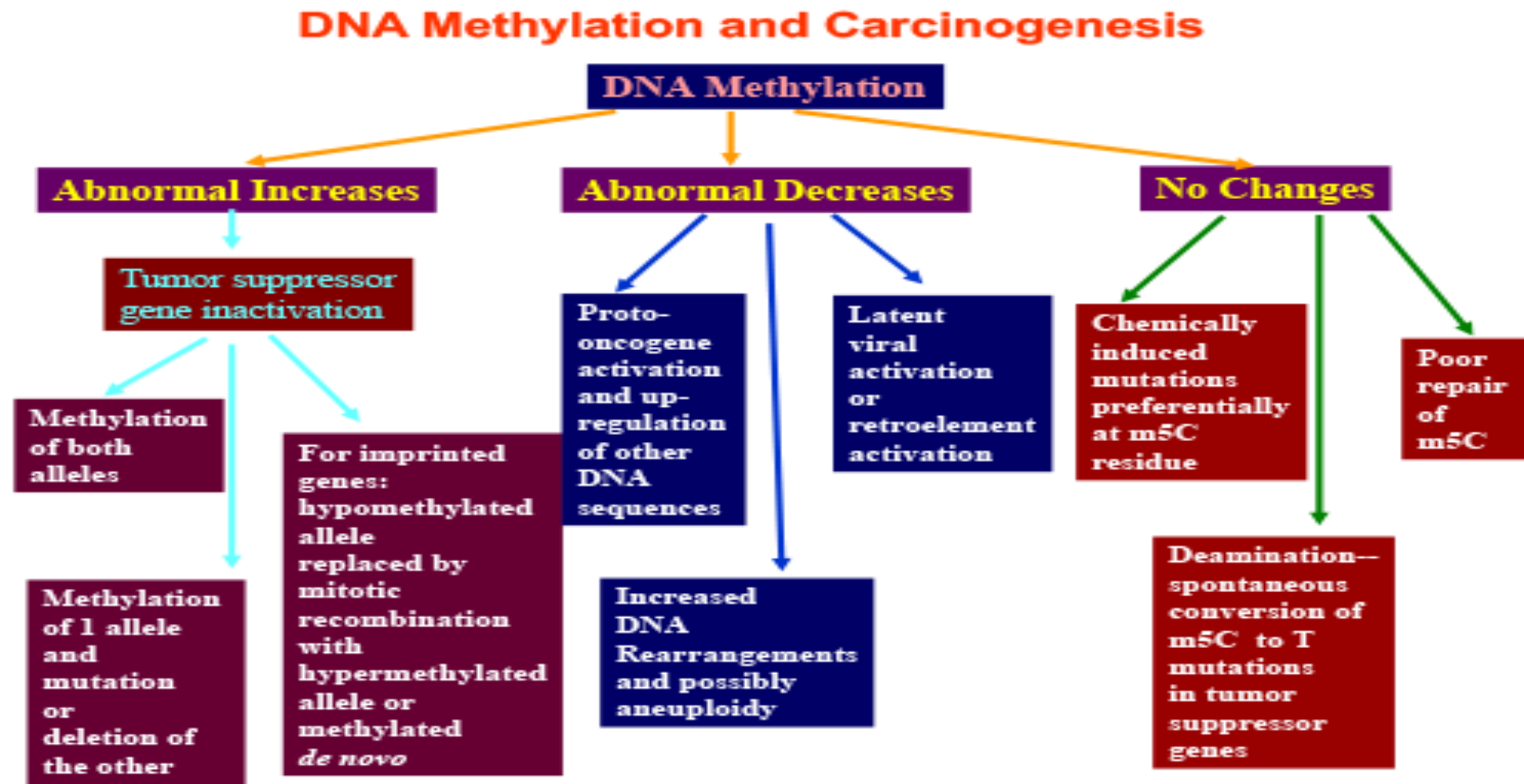
Tumor alterations



Genetic mutations

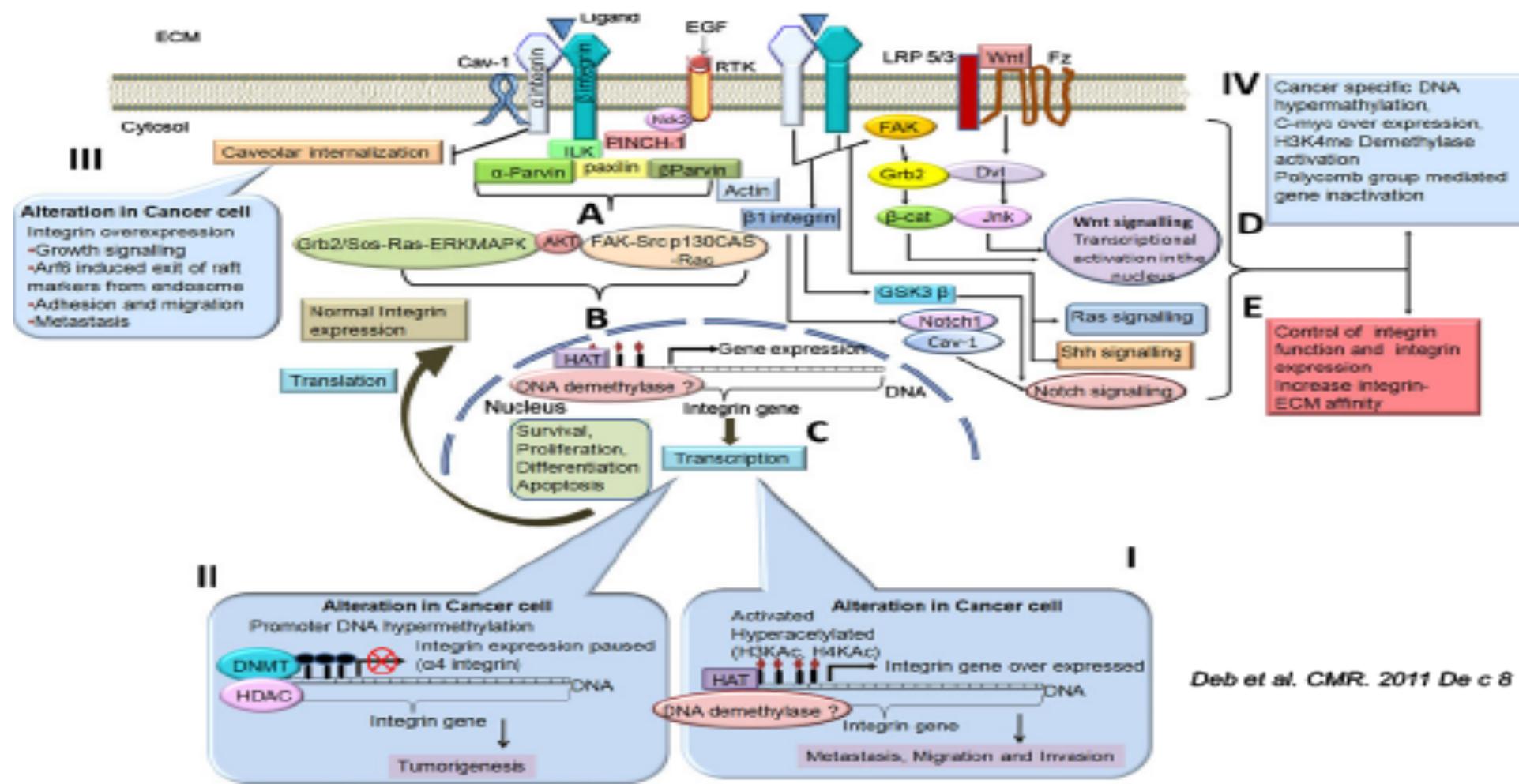


DNA methylation and carcinogenesis



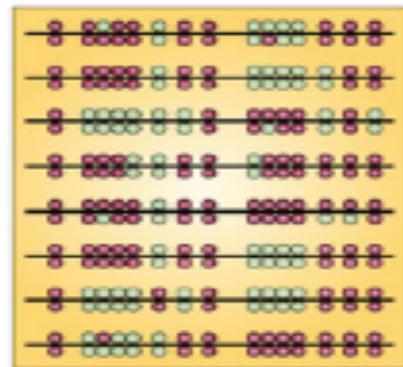
Integrin signaling

Integrin Signaling Network and Epigenetic Regulation

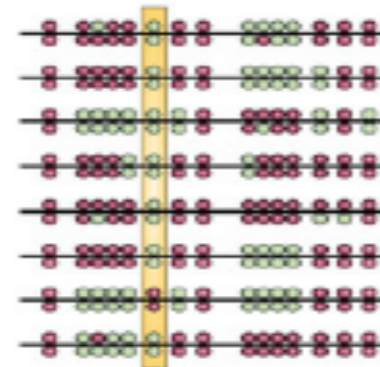


Methylation

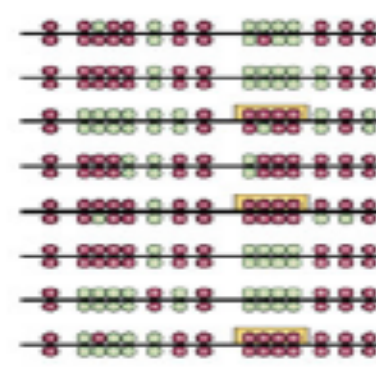
a Methylation content



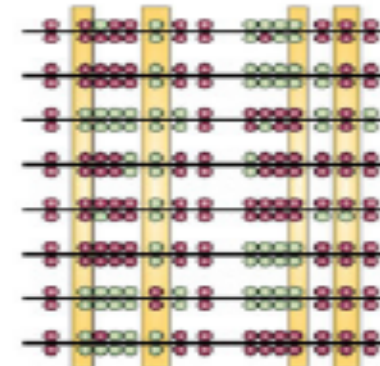
b Methylation level



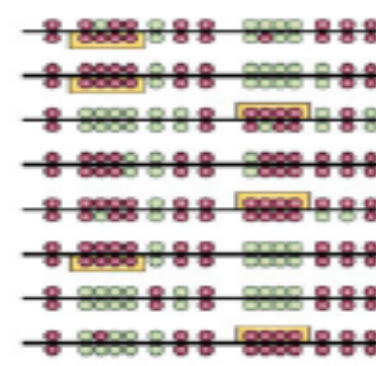
c Methylation pattern



d Level profile



e Pattern profile

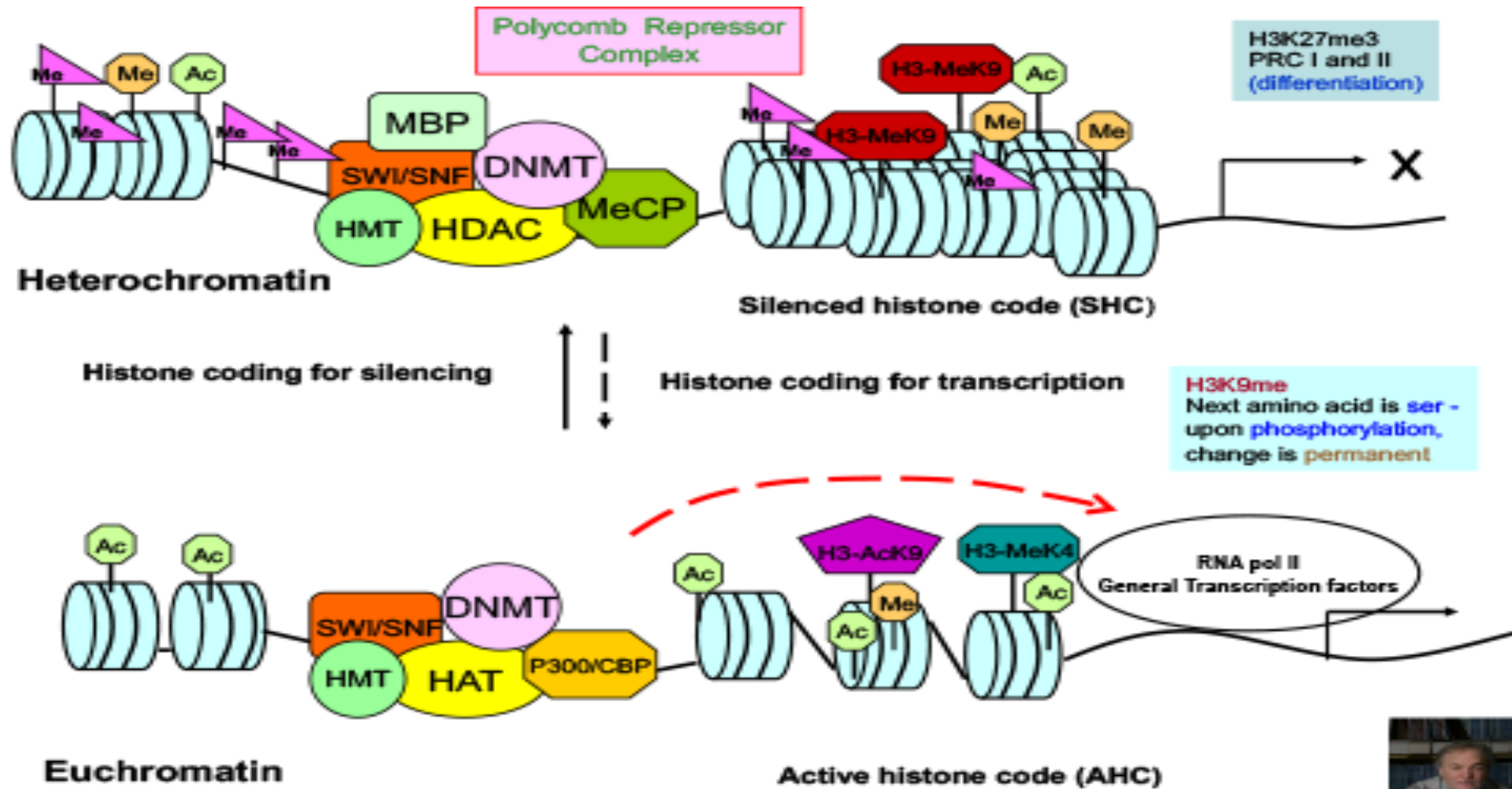


- Total methylation content of the cell
- methylation level at specific stage
- methylation pattern of a group of genes
- profile of methylation of either a specific gene or a number of genes
- pattern of methylation in the whole epigenome

To reduce

- false negative
- false positives

Histone acetylation



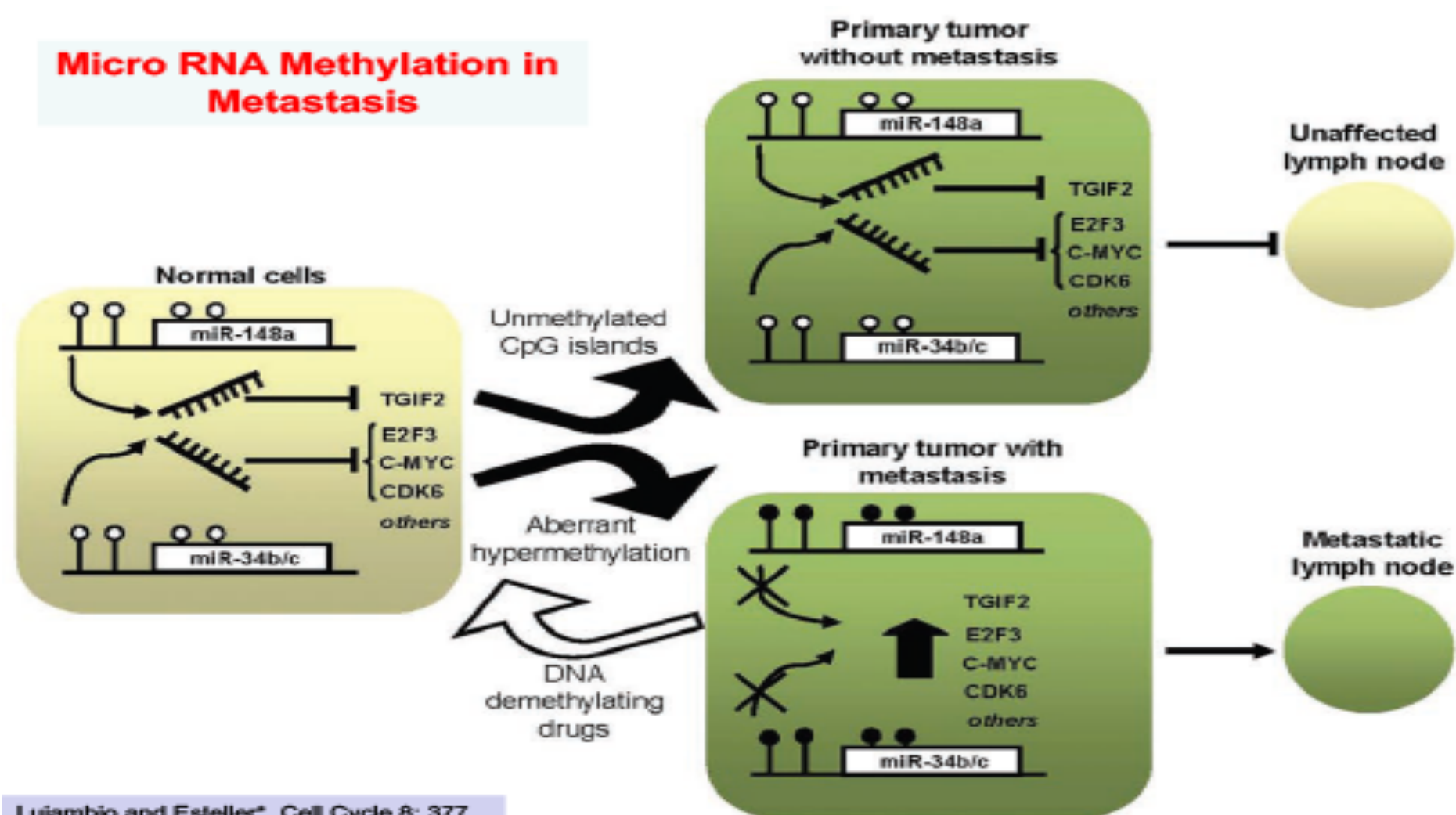
Micro RNA signatures

Mirco RNA Signatures in Human Cancers



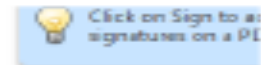
Micro RNA Polymorphism to Identify High Risk Populations

Micro RNA methylation



Extracellular vesicles

Verma et al. *BMC Clinical Pathology* (2015) 15:6
DOI 10.1186/s12907-015-0005-5



REVIEW

Open Access

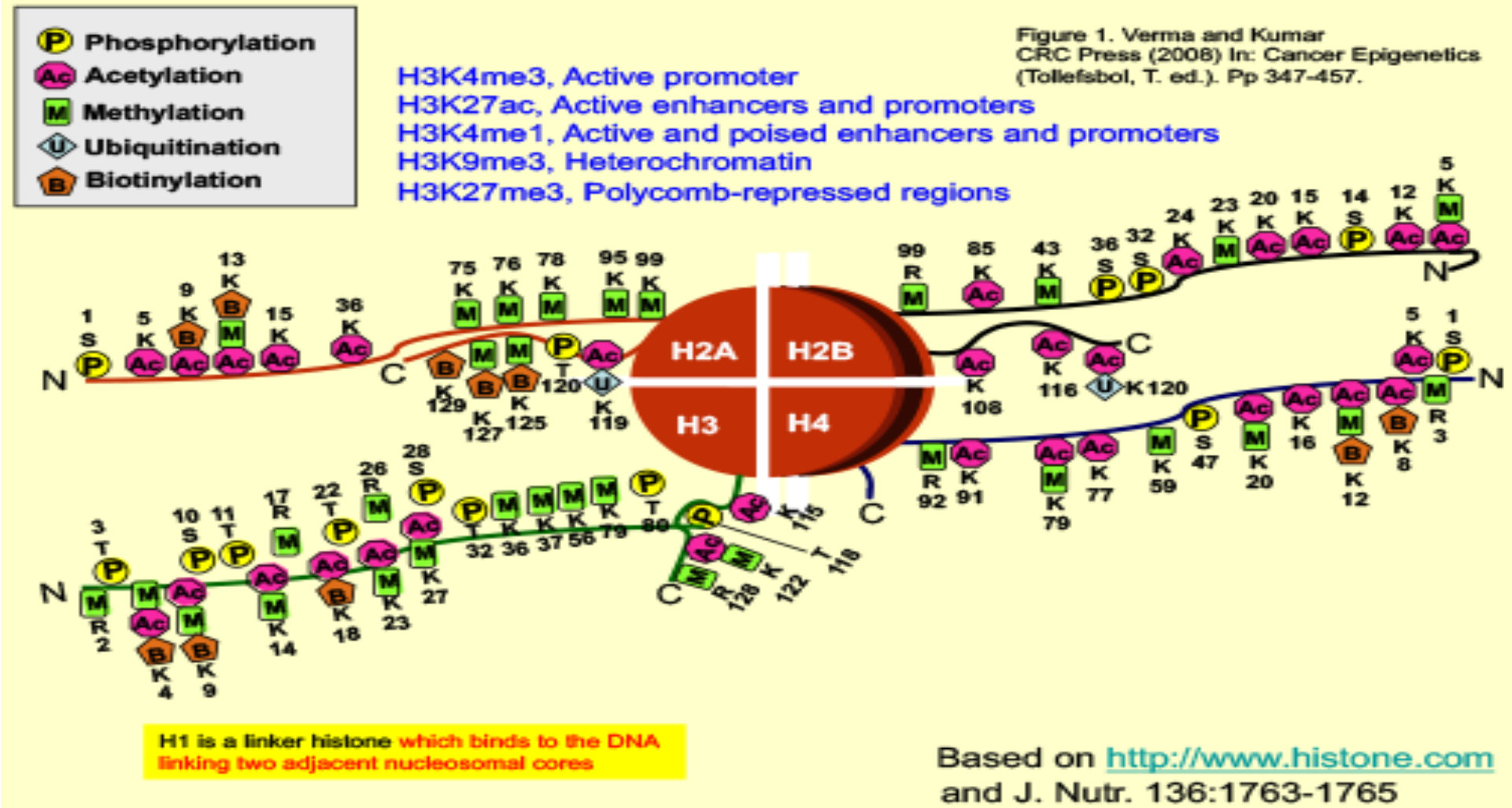
Extracellular vesicles: potential applications in cancer diagnosis, prognosis, and epidemiology

Mukesh Verma^{*}, Tram Kim Lam, Elizabeth Hebert and Rao L. Divi

Abstract

Both normal and diseased cells continuously shed extracellular vesicles (EVs) into extracellular space, and the EVs carry molecular signatures and effectors of both health and disease. EVs reflect dynamic changes that are occurring in cells and tissue microenvironment in health and at a different stage of a disease. EVs are capable of altering the function of the recipient cells. Trafficking and reciprocal exchange of molecular information by EVs among different organs and cell types have been shown to contribute to horizontal cellular transformation, cellular reprogramming, functional alterations, and metastasis. EV contents may include tumor suppressors, phosphoproteins, proteases,

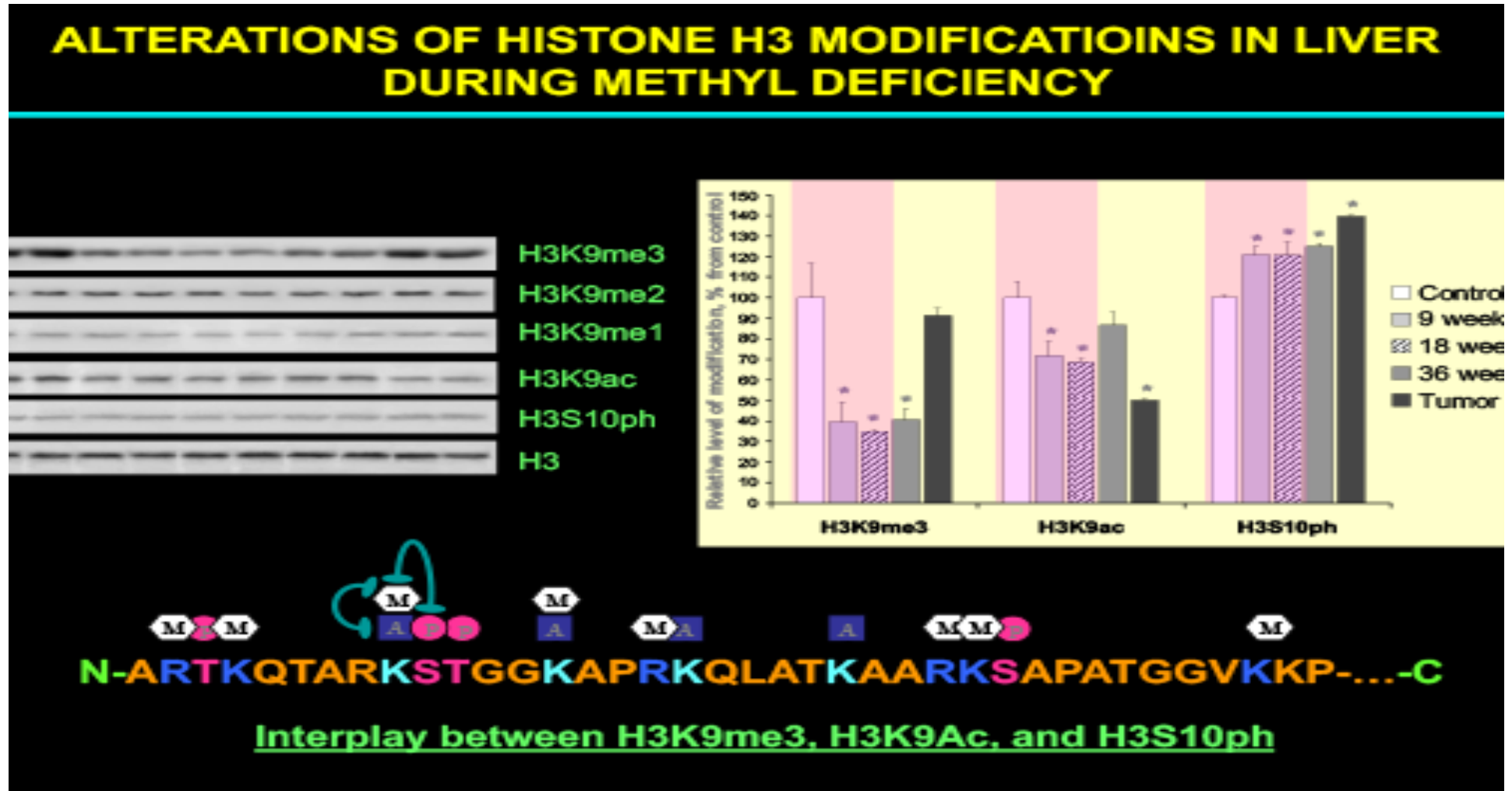
Histone modifications



Histones



Histone H3 modifications



Epigenetic regulation

Epigenetic Gene Regulation:

Modification		Methylation			Acetylation
		Mono-methylation	Di-methylation	Tri-methylation	
DNA		Repression	--	--	--
Histone	H3K4	Activation	Activation	Activation	--
	H3K9	Activation	Repression	Repression	Activation
	H3K27	Activation	Repression	Repression	--
	H3K36	--	Repression	Activation	Activation
	H3K79	Activation	Activation	Activation Repression	--
	H3R17	--	Activation	--	--
	H4K5	--	--	--	Activation
	H4K8	--	--	--	Activation
	H4K12	--	--	--	Activation
	H4K16	--	--	--	Activation
	H4K20	Activation	Activation	Repression	--
	H4K16	--	--	--	Activation



Single cell epigenomics

SINGLE CELL EPIGENOMICS

Single cells isolated from

- Blood
- Breast milk
- Exfoliated cells
- Hair
- Oral swab
- Pancreatic fluid
- Saliva
- Skin
- Tissue
- Urine

1. Methylation profiling
2. Histone modifications
3. miRNA profiling
4. Chromatin Accessibility

Single Cell
Epigenomics

Identify open and closed chromatin

Identify cell-specific transcription factors

Determine nucleosome position

Identify active and repressive
transcription state

Implications of single cell epigenomics

Risk Assessment to identify high-risk individuals
Diagnosis
Prognosis
Screening
Follow up treatment and co-morbidity

Histone modifications

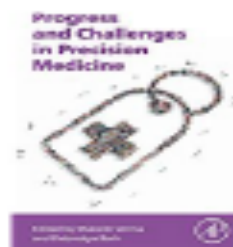
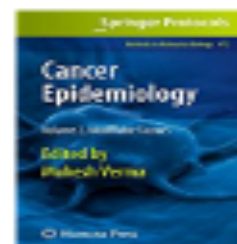
20 Diagnosing Cancer Using Histone Modification Analysis

Mukesh Verma and Deepak Kumar

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Books



Books edited by Mukesh Verma

Epigenetic changes

Epigenetics: travelling the cancer road

DNA with increased methylation and hypothesized that if a tumour suppressor gene was hypermethylated, its activity would decrease or stop entirely — just as if it were a genetic mutation — allowing the tumour to flourish. In other words, Baylin reasoned, this epigenetic change would produce the same result as a genetic mutation.

Firm evidence came in 1994. Baylin and his colleague, oncologist James Herman, were investigating renal cell carcinoma (RCC), the most common type of kidney cancer in adults. Around 60% of RCCs are caused by an inherited mutation in the von-Hippel-Lindau tumour-suppressor gene (VHL), which hobbles the gene's ability to express the tumour suppressing protein. Baylin and Herman showed that 20% of the remaining non-inherited form of RCC did so have a mutation in VHL. Their genes were silenced not by mutation, but rather by hypermethylation².

The following year, in collaboration with Sidransky's lab at Johns Hopkins, Baylin and his colleagues showed that human cancers commonly arise when a particular tumour suppressor gene, known as p16, is inactivated. Moreover, in many cancers including RCC, epigenetic and genetic mutations often work together. In some cases, one copy of a tumour suppressor gene is inactivated by genetic mutation, while the other copy is silenced by hypermethylation. This finding "convinced us that epigenetic abnormalities could play an important driving role in cancer, and many others have been pursuing this possibility ever since," says Baylin.

The move from a purely genetic to an epigenetic model is crucial for prevention strategies. As numerous gene therapy trials have shown, it is very difficult to treat a genetic disease by re-activating the dormant, mutated gene or by replacing it with a non-mutated one. "Epigenetic changes are reversible, and therefore have an edge over genetics," says Mukesh Verma, an epigeneticist at the National Cancer Institute's division of cancer control and population sciences in Bethesda, Maryland. Furthermore, epigenetic changes in cancer occur before genetic mutations. "If you can prevent methylation of those tumour suppressor genes, you might have a valuable prevention strategy," says Baylin.

The environmental link

Epigenetics has also provided clues that link environmental factors with cancerous genetic changes. Changes in methylation can be detected in the blood of cancer-free individuals who smoke and eat high-fat diets, and these

Epigenetic changes are reversible, and therefore have an edge over genetics"
Mukesh Verma
Nature 471: s12-s13

Epigenetic changes are reversible, and therefore have an edge over genetics," says Mukesh Verma, an epigeneticist at the National Cancer Institute's division of cancer control and population sciences in Bethesda, Maryland. Furthermore, epigenetic changes in cancer occur before genetic mutations. "If you can prevent methylation of those tumour suppressor genes, you might have a valuable prevention strategy," says Baylin.

Epigenetic drugs

The image is a screenshot of a web browser displaying a Nature article titled "Epigenetics: Marked for success". A red rectangular box highlights a specific paragraph in the article. A blue speech bubble callout points to this highlighted text, containing a quote from Mukesh Verma. To the right of the callout, a green rectangular box contains the citation "Nature 483:637-639".

Epigenetics: Marked for success: Nature | Mozilla Firefox

http://www.nature.com/news/epigenetics/040110/1.0011001-607a

Epigenetics: Marked for success: Nat...

programmers could do around 200 jobs. The bulk of the funding for these large-scale programmes is already dedicated to the larger sequencing centres, but smaller teams are using the data from these projects to generate individual investigator grant applications. Shaw adds.

These data have helped to persuade investors in industry that epigenetic abnormalities in cancer are a wealth of new drug targets. The finding that mutations in epigenetic-related genes may be driving cancer offers the tantalizing possibility of taking a personalized approach to cancer treatment, a tack that is rapidly gaining ground in industry, says Robert Gould, chief executive of Epizyme, an epigenetics-focused biotechnology firm based in Cambridge, Massachusetts. This evidence, plus the successful approval of a first generation of drugs intended to target epigenetic pathways, has convinced almost every major drug company to invest in cancer epigenetics, says Mukesh Verma, a programme officer at the NCI. For example, Novartis, a pharmaceutical firm with its headquarters in Basel, Switzerland, has more than 200 employees working in epigenetics, most of them in cancer, says En Li, head of China Novartis Institutes for Biomedical Research, based in Shanghai. Last year, GlaxoSmithKline in London, in addition to funding its own epigenetics team, paid \$20 million to partner with Epizyme in a deal in which Epizyme could ultimately receive as much as \$600 million. "GSK's group is partnering with us and is also competing with us on other programmes," says Epizyme's chief scientific officer, Robert Copeland. "It makes for an interesting dynamic."

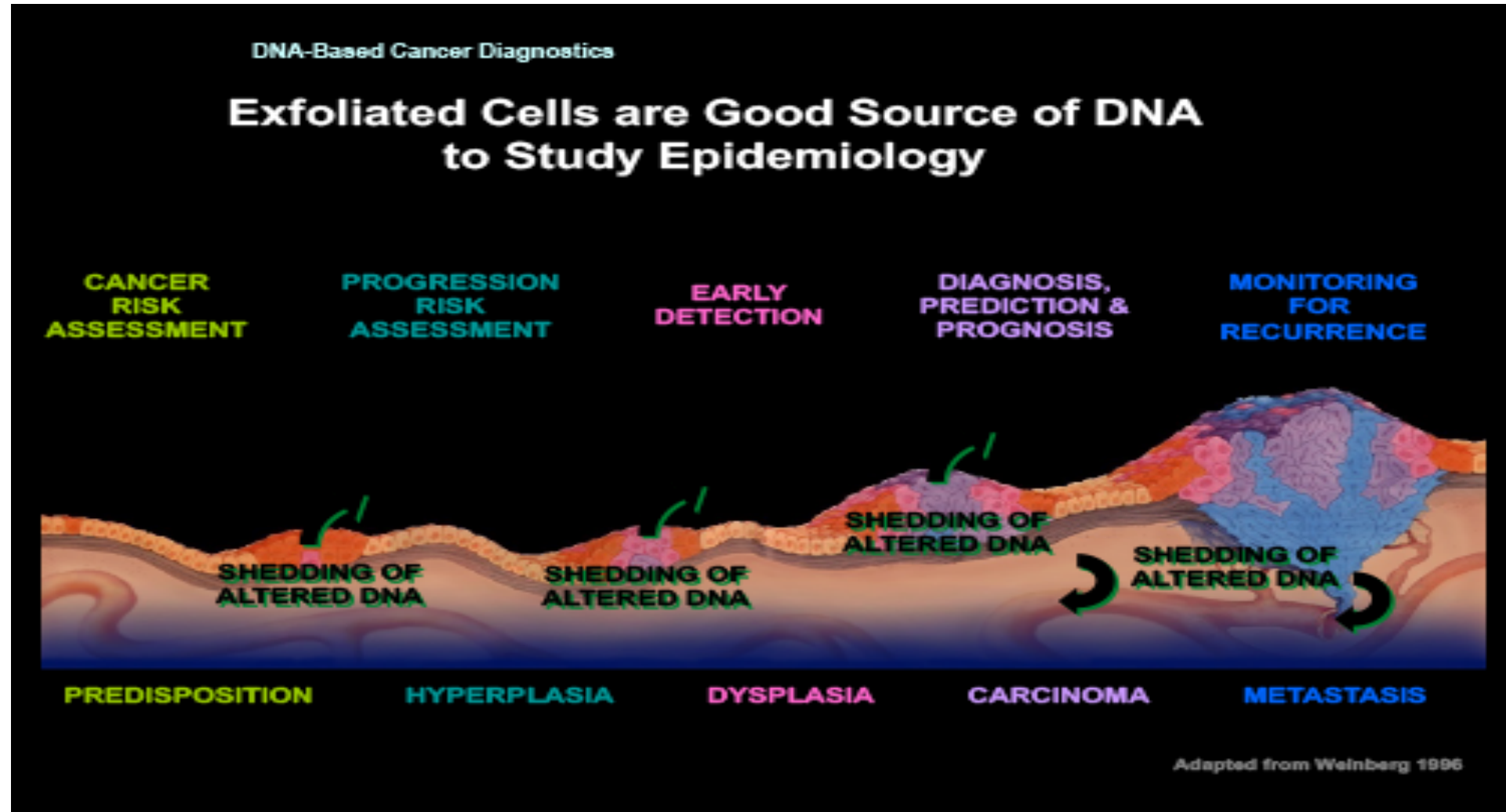
With so much excitement, competition in the field can be fierce. Data from large government projects can be a boon to smaller labs, says Clark, but individual investigators and those new to the field need to carve their own niche. "In the face of those big initiatives, smaller labs have the challenge of asking smaller and more unique questions as to the basic mechanisms underlying these epigenetic changes," she says. Christopher Vakoc, an epigenetics researcher at Cold Spring Harbor Laboratory in New York, notes that the "tiny" lab he started in 2008 directly competed with several big pharmaceutical companies to discover a role for Bmi1 — a "reader" protein that binds to certain modified histones and modulates gene expression — in acute myeloid leukaemia ([J. Zuber et al. Nature 478, 534–538; 2011](#)). After his team's paper was published, Vakoc heard rumours that the companies were racing to capitalize on the results.

There is also an intense demand for talent. In particular, epigenetics companies and individual labs need

"Successful approval of first generation of drugs intended to target epigenetic pathways, has convinced almost every major drug company to invest in cancer epigenetics."
Mukesh Verma

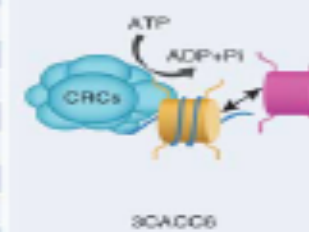
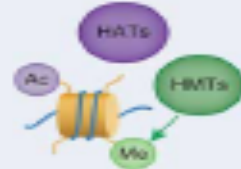
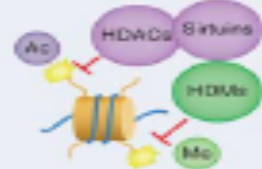
Nature 483:637-639

Exfoliated cells



Histone enzymes

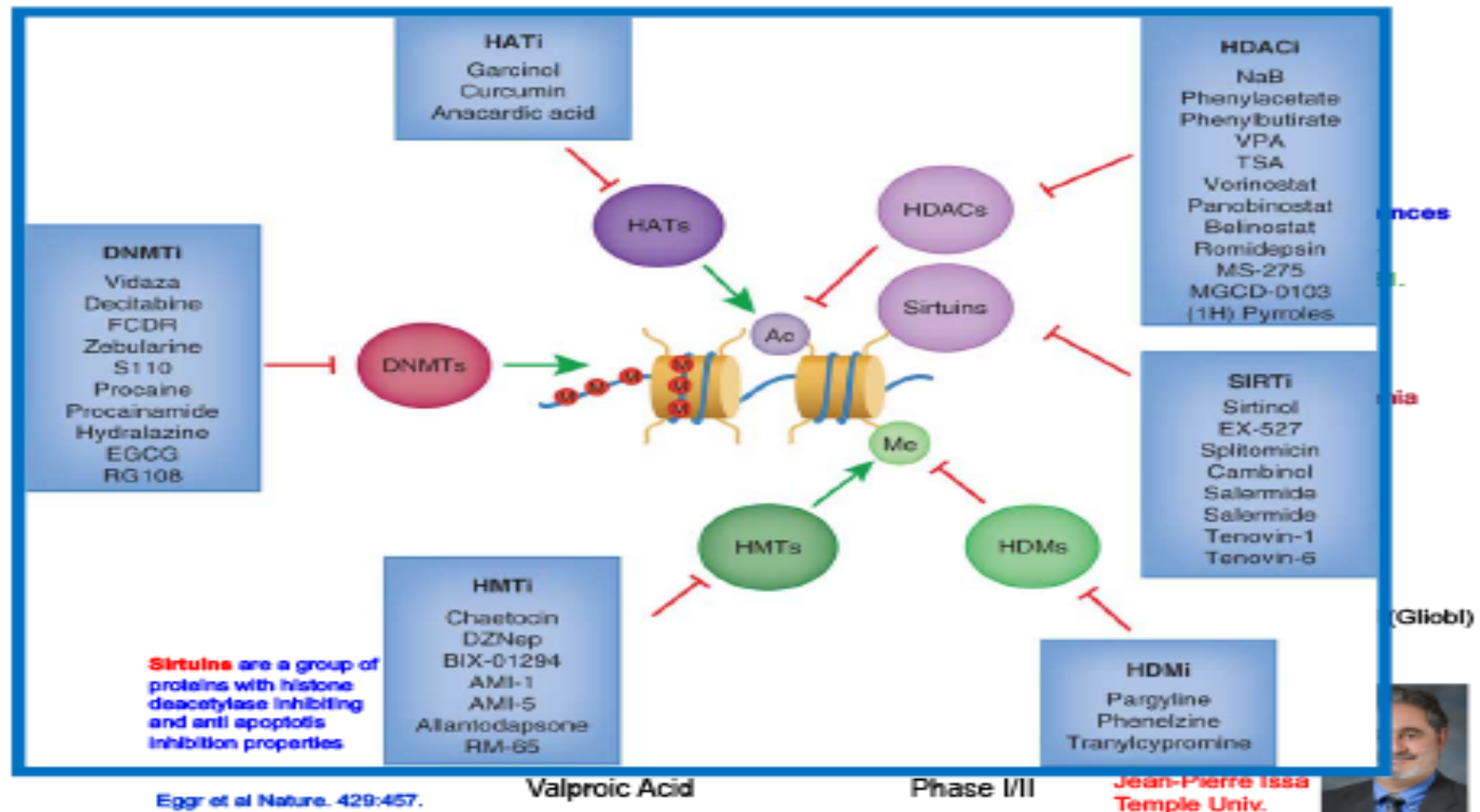
TUMOR		GENE		
Category	Gene	Category	Gene	
HDACs	HDAC1	DNMTs	DNMT1	
	HDAC2		DNMT3A	
	HDAC6		DNMT3B	
Sirtuins	SIRT1	(2OG)-Fe(II)-dependent oxygenases	TET1	
	SIRT2		TET2	
	SIRT3	Methyl-CpG binding proteins	MBD1	
	SIRT7		MBD2	
HDMs	KDM1A		MBD3	
	KDM2B		MBD4	
	KDM4C		MECP2	
	KDM5A			
	KDM5B			
	KDM5C			
KDM6A				
KDM6B				
Category	Gene	Category	Gene	
HATs	CREBBP	Histone variants	H2AFZ	
	EP300		ARID1A	
	MYST3		CHD5	
	MYST4		CHD7	
HMTs	KAT5		Chromatin remodeling factors	MTA1
	MLL			MTA2
	EZH2	MTA3		
	NSD1	SMARCA2		
	PRDM2	SMARCA4		
	SMYD3	SNF5		
WHSC1				
Category	Gene	Category	Gene	
Histone modification readers	ING1	Histone modification readers	ING1	
	ING2		ING2	
	ING3		ING3	
	ING4		ING4	
	ING5		ING5	



Sirtuins are a group of proteins with histone deacetylase inhibiting and anti apoptosis inhibition properties

Verma and Srivastava (2002). *Lancet Oncol.* 3: 755-363;
Verma et al (2004). *Crit. Rev. Clin. Sc.* 41: 585-607;
Verma and Manne (2006). *Crit. Rev. Hematol. Oncol.* 60: 9-18;
Verma et al (2006). *Mol. Diag. Therapy.* 10: 1-15.

Methylation and acetylation enzymes



HDAC inhibitors

- HDAC inhibitors are a novel class of anticancer drugs that mainly leads to an accumulation of acetylated proteins

Thereby inducing

- Cell cycle arrest
 - Differentiation
 - Migration
 - apoptosis in cancer and transformed cells
- Few HDAC inhibitors act as radiation-sensitizing drugs resulting in better radiation therapy (head and neck cancer) responsiveness

HDAC 1, 2, 3, 8, 11 have been characterized (Khan, I , 2007)

Phase I study

Phase I study of epigenetic modulation with 5-azacytidine and valproic acid in patients with advanced cancers.

Braiteh F, Soriano AO, Garcia-Manero G, Hong D, Johnson MM, Silva Lde P, Yang H, Alexander S, Wolff J, Kurzrock R. Clin Cancer Res.14(19):6296-301. (colorectal cancer, melanoma and breast cancer)

5 Azacytidine
S.C. daily for 10 days

+

Valproic Acid
Orally daily to titrate
to 75-100 ug/ml



Peripheral blood
• Pyrosequencing
• Chip

Analysis
Day 1, 10 and 28

28 Days Cycle

55 people with
Advanced cancer
Median age 60

- The maximum tolerated dose was 75 mg/m² of 5-AZA in combination with valproic acid.

- Dose-limiting toxicities were neutropenic fever and thrombocytopenia, which occurred at a dose of 94 mg/m² of 5-AZA.

- Stable disease lasting 4 to 12 months (median, 6 months) was observed in 14 patients (25%).

A significant decrease in global DNA methylation and induction of histone acetylation were observed.

The combination of 5-AZA and valproic acid is safe at doses up to 75 mg/m² for 5-AZA in patients with advanced malignancies.

5-azacytidine, valproic acid and ATRA

Safety and clinical activity of the combination of 5-azacytidine, valproic acid, and all-trans retinoic acid in acute myeloid leukemia and myelodysplastic syndrome.

Soriano et al. Blood. 110(7):2302-8.

- Combination of 5-azacytidine (5-AZA), valproic acid (VPA), and ATRA in patients with acute myeloid leukemia or high-risk myelodysplastic syndrome.
- A total of 53 patients were treated.
- The overall response rate was 42%.
- A significant decrease in global DNA methylation and induction of histone acetylation were achieved.
- VPA blood levels were higher in responders.
- The combination studied is safe and has significant clinical activity.

This clinical trial was registered at www.clinicaltrials.gov as no. NCT00326170.

Histone inhibitors

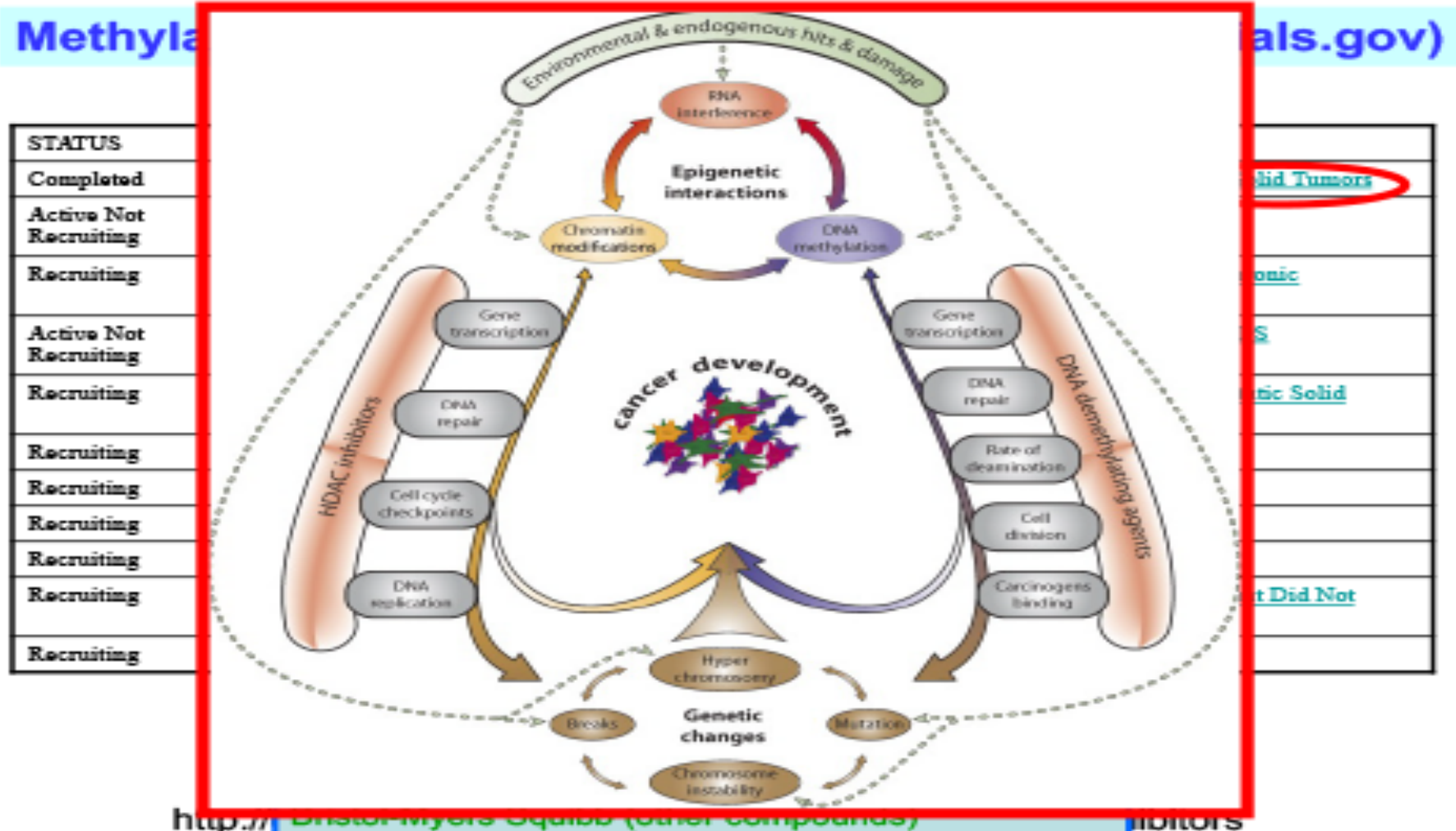
Histone Inhibitors in Clinical Trials (Clinicaltrials.gov)

STATUS	STUDY
Recruiting	Safety Study of the Histone Deacetylase Inhibitor, CHR-3996, in Patients With Advanced Solid Tumours
Recruiting	Phase II Study of Histone-Deacetylase Inhibitor ITF2357 in Refractory/Relapsed Lymphocytic Leukemia
Recruiting	pHII Study of an HDAC Inhibitor in Very High-Risk Relapsed/Refractory Hodgkin's Lymphoma Patients
Recruiting	Phase IIA Study of the HDAC Inhibitor ITF2357 in Patients With JAK-2 V617F Positive Chronic Myeloproliferative Diseases
Recruiting	Phase II Trial of the Histone-Deacetylase Inhibitor ITF2357 Followed by Mechlorethamine in Relapsed/Refractory Hodgkin's Lymphoma Patients
Recruiting	HDAC Inhibitor Vorinostat (SAHA) With Capecitabine (Xeloda) Using a New Weekly Dose Regimen for Advanced Breast Cancer
Recruiting	Valproic Acid, Temozolomide, and Radiation Therapy in Treating Patients With Glioblastoma Multiforme
Recruiting	Study of Vorinostat (MK0683) an HDAC Inhibitor, or Placebo in Combination With Bortezomib in Patients With Multiple Myeloma
Recruiting	Study of Vorinostat (MK0683), an HDAC Inhibitor, in Combination With Bortezomib in Patients With Relapsed or Refractory Multiple Myeloma
Completed	A Phase II Study of Epigenetic Therapy to Overcome Chemotherapy Resistance in Refractory Solid Tumors
Recruiting	Sorafenib and LBH589 in Hepatocellular Carcinoma (HCC)
Recruiting	Phase II Study of Valproic Acid With FEC100 for Patients With Locally Advanced Breast Cancer

Total : 84 studies

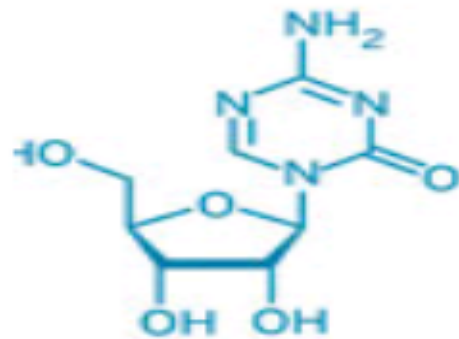
<http://clinicaltrials.gov/ct2/results?term=histone+inhibitors&pg=4>

Environmental damage

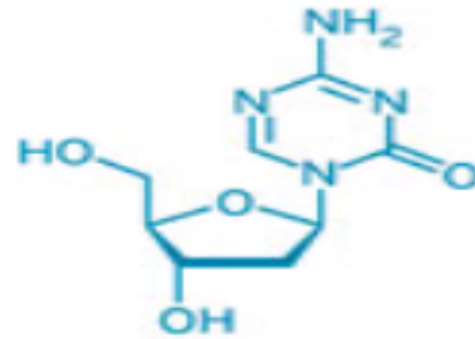


Epigenetic inhibitors

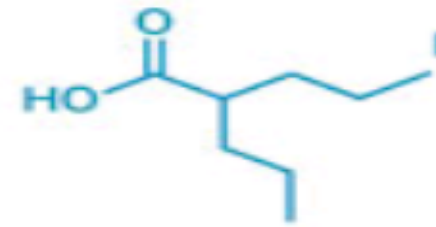
FDA Approved Epigenetic Inhibitors



5-Azacitidine



Decitabine

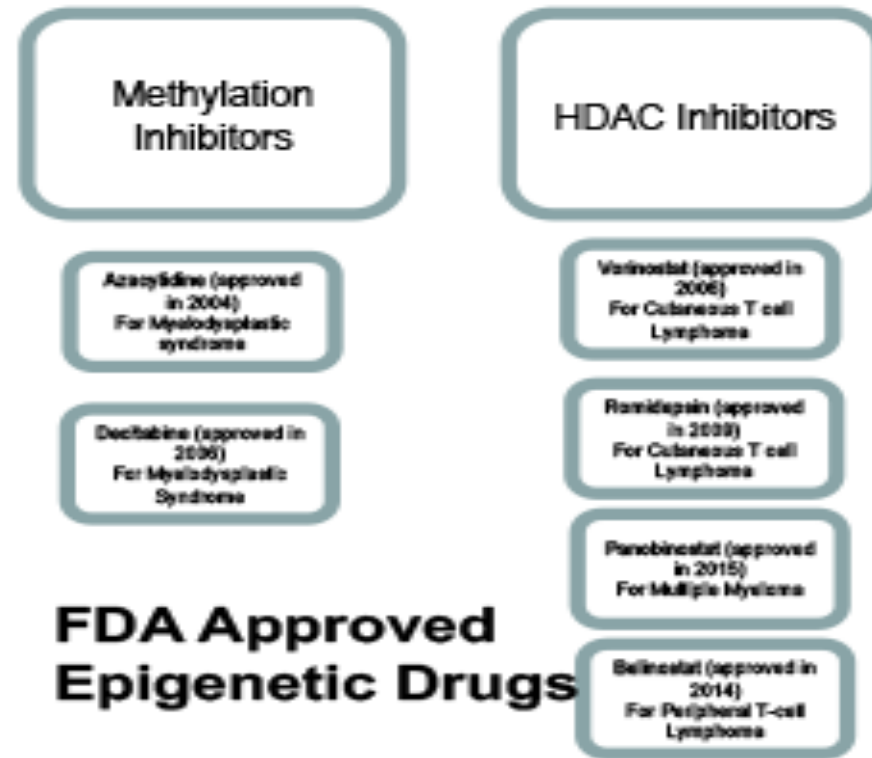


Valproic acid



SAHA

Approved epigenetic drugs



Epigenetic drugs

Cancer type	Epigenetic therapy	Drug combination	Patient selection	Response	Pharmacodynamic target validation ^{†*}	Refs [‡]
Gastrointestinal stromal tumours	Paritumumab (pan-EGFR inhibitor)	Paritumumab and imatinib	Patients with metastatic gastrointestinal stromal tumours refractory to imatinib and sunitinib	1 of 11 partial response; 7 of 11 stable disease; 3 of 11 progressive disease	Yes	87
Wild-type KRAS metastatic colorectal cancer	Decitabine (demethylating agent)	Decitabine and panitumumab (monoclonal antibody against EGFR)	Patients with progressive disease on standard therapy and previously treated with cetuximab	2 of 20 partial response; 11 of 20 stable disease; 7 of 20 progressive disease	No	88
Advanced solid tumours	Azacitidine (demethylating agent); Valproic acid (pan-EGFR inhibitor)	Azacitidine, valproic acid and carboplatin	Advanced cancer and progression following standard therapy (platinum-based) or no standard effective therapy available	6 of 32 stable disease; 26 of 32 progressive disease	Yes	89
Epithelial ovarian cancer	Decitabine (demethylating agent)	Decitabine and carboplatin	Initial response by RECIST and/or CA125 criteria then progressing 6–12 months after previous platinum therapy	3 of 15 CA125 partial response; 1 of 15 RECIST partial response	Yes	78
Epithelial ovarian cancer	Decitabine (demethylating agent)	Decitabine and carboplatin	Progression or recurrence within 6 months of platinum-based compound	1 of 17 complete response; 5 of 17 partial response	Yes	77
Epithelial ovarian cancer	Azacitidine (demethylating agent)	Azacitidine and carboplatin	Progression or recurrence within 6 months of platinum-based compound	1 of 29 complete response; 3 of 29 partial response	Yes	90
Prostate cancer	Azacitidine (demethylating agent)	Azacitidine, LHRH analogue and anti-androgens	Progression on combined androgen blockade	19 of 34 PSADT >3 months; 11 of 34 PSADT >6 months; 9 of 34 PSADT >9 months	Yes	91
ER- and PR-positive breast cancer	Vorinostat (pan-EGFR inhibitor)	Vorinostat and tamoxifen	Progression or recurrence on any endocrine inhibitors or completed tamoxifen for 1 year	8 of 34 partial response	Yes	92
Epithelial ovarian cancer	Belinostat (pan-EGFR inhibitor)	Belinostat and carboplatin	Recurrence at ≤6 months of last platinum and taxol treatment	2 of 27 objective response	No	93
Epithelial ovarian cancer	Belinostat (pan-EGFR inhibitor)	Belinostat, carboplatin and paclitaxel	Platinum-refractory or -resistant disease	15 of 35 objective response	No	94

EGFR, epidermal growth factor receptor; ER, estrogen receptor; LHRH, luteinizing hormone-releasing hormone; PR, progesterone receptor; PSADT, prostate specific antigen doubling time; RECIST, response evaluation criteria in solid tumors. [†]Pharmacodynamic validation refers to whether there was evidence of epigenetic responses in surrogate or tumour tissue from patients. [‡]Publications were identified using PubMed. Search terms: HDAC inhibitors, decitabine or 5-azacytidine or azacitidine or 5-azacytidine or demethylating agent and cancer. Only clinical trials of solid tumours that used a chemotherapy agent that patients are already known to be resistant to are included.

Combination therapy

AML subtypes and combination therapy



Pharmaceutical Participation

AML Subtype	Drug	Company
Tet2/WT1	CD33 + Aza	BI
IDH2 Mutation	Enasidenib	Celgene
MLL	Entospletinib (Syk inhibitor)	Gilead
CBF	Samalizumab (CD200 Ab) + induction	Alexion
P53 mutation	Entospletinib (Syk inhibitor) + Decitabine	Gilead
Complex Karotype	Entospletinib (Syk inhibitor) + Decitabine	Gilead
P53 mutation	Pevonedistat (Nedd8 inhibitor) + Aza	Takeda
Marker Negative	CD33 + Aza	BI
NPM1 w FLT3 WT	Entospletinib (Syk inhibitor)	Gilead
FLT3 mutation	Gilteritinib	Astellas
IDH1 Mutation	Ivosidenib + Aza	Agios

Source: Leukemia & Lymphoma Society

Cancer letters 17 July 2018

Epigenetic therapy



Click on Sign to add text and place signatures on a PDF file.

Chapter 40

Epigenetic Therapy for Colorectal Cancer

Vivek Vaish, Tripti Khare, Mukesh Verma, and Sharad Khare

Abstract

Aberrations in epigenome that include alterations in DNA methylation, histone acetylation, and miRNA (and/or DKK1) expression may account for the progression of colorectal cancer (CRC). These epigenetic changes

Combination epigenetic therapy

Combination epigenetic therapy has efficacy in... [Cancer Discov. 2011] - PubMed - NCBI

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http://www.ncbi.nlm.nih.gov/pubmed/22586602

NCBI Resources How To

PubMed US National Library of Medicine National Institutes of Health

Advanced

Display Settings: Abstract Send to:

Cancer Discov. 2011 Dec;1(7):598-607. doi: 10.1158/2159-8290.CD-11-0214. Epub 2011 Nov 9.

Combination epigenetic therapy has efficacy in patients with refractory advanced non-small cell lung cancer.

Jurgens BA, Wrangle J, Vendetti EP, Murphy SC, Zhao M, Coleman B, Sebree R, Rodgers K, Hooker CM, Franco N, Lee B, Tsai S, Delgado JE, Rudik MA, Belinsky SA, Herman JG, Baylin SB, Brock MV, Rudin CM.

Department of Oncology, Johns Hopkins University, Baltimore, Maryland 21231, USA.

Abstract

Epigenetic alterations are strongly associated with the development of cancer. We conducted a phase III trial of combined epigenetic therapy with azacitidine and entinostat, inhibitors of DNA methylation and histone deacetylation, respectively, in extensively pretreated patients with recurrent metastatic non-small cell lung cancer. This therapy is well tolerated, and objective responses were observed, including a complete response and a partial response in a patient who remains alive and without disease progression approximately 2 years after completing protocol therapy. Median survival in the entire cohort was 6.4 months (95% CI 3.8-9.2), comparing favorably with existing therapeutic options. Demethylation of a set of 4 epigenetically silenced genes known to be associated with lung cancer was detectable in serial blood samples in these patients and was associated with improved progression-free (P = 0.034) and overall survival (P = 0.035). Four of 19 patients had major objective responses to subsequent anticancer therapies given immediately after epigenetic therapy. Significance: This study demonstrates that combined epigenetic therapy with low-dose azacitidine and entinostat results in objective, durable responses in patients with solid tumors and defines a blood-based biomarker that correlates with clinical benefit.

Comment in

A combined epigenetic therapy equals the efficacy of conventional chemotherapy in refractory advanced non-small cell lung cancer. [Cancer Discov. 2011]

PMID: 22586602 [PubMed - indexed for MEDLINE] PMCID: PMC3353726 [Available on 2012/12/1]

Publication Types, MeSH Terms, Substances, Grant Support

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Related citation

Randomized phase III trial of combination therapy with docetaxel, irinotecan, and cetuximab without epirubicin in patients with advanced non-small-cell lung cancer: a North Central Cancer Treatment Group study. *J Clin Oncol*. 2011 Nov 15;29(46):5853-5862. doi: 10.1200/JCO.2011.39.2000. Epub 2011 Nov 9.

14-3-3sigma mediates the effect of 14-3-3sigma on the expression of 14-3-3sigma target genes. *J Biol Chem*. 2011 Nov 9;286(45):39533-39542. doi: 10.1074/jbc.M111.200000. Epub 2011 Nov 9.

Cited by 1 PubMed

2-Deoxyribose and 2-Deoxythymine in the presence of 2-Deoxyribose 5-phosphate. *J Biol Chem*. 2011 Nov 9;286(45):39533-39542. doi: 10.1074/jbc.M111.200000. Epub 2011 Nov 9.

Low doses of DNA-demethylating agents

et al. 2012 Barlin cancer treatment Cell Science.pdf - Adobe Reader

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Cell PRESS

Cancer Cell
Article

Transient Low Doses of DNA-Demethylating Agents Exert Durable Antitumor Effects on Hematological and Epithelial Tumor Cells

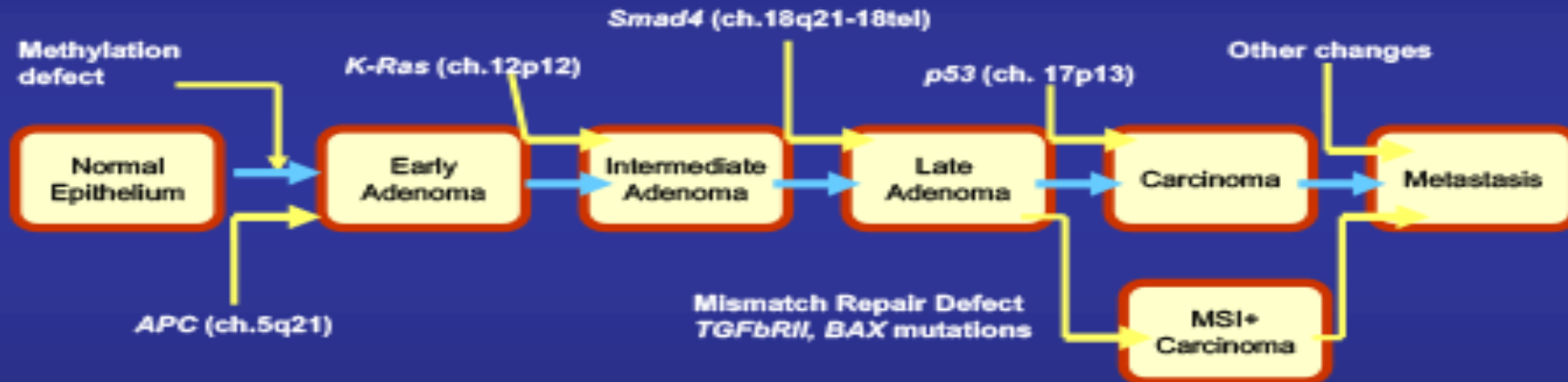
Hsing-Chen Tsai,^{1,2,10} Huili Li,^{2,10} Leander Van Neste,^{2,10} Yi Cai,² Carine Robert,⁴ Foyruz V. Rassool,⁴ James J. Shin,^{2,5} Kirsten M. Harbom,² Robert Beaty,² Emmanouil Pappou,^{2,5} James Harris,^{2,5} Ray-Whay Chiu Yen,² Nita Ahuja,^{2,5} Malcolm V. Brock,^{2,5} Vered Stearns,^{2,5} David Feller-Kopman,⁷ Lonny B. Yarmus,⁷ Yi-Chun Lin,⁸ Alana L. Weim,⁸ Jean-Pierre Issa,⁹ Il Minn,² William Matsui,^{1,2} Yoon-Young Jang,² Saul J. Sharkis,^{1,2} Stephen B. Baylin,^{1,2,*} and Cynthia A. Zahnow^{2,5,*}

¹The Graduate Program in Cellular and Molecular Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA
²The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD 21231, USA
³MDxHealth PharmacoDx BVBA, Technologiepark 4, 9052 Ghent, Belgium
⁴Department of Radiation Oncology, Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD 21201, USA
⁵Department of Surgery, School of Medicine, Johns Hopkins University, Baltimore, MD 21231, USA
⁶Breast Cancer Program, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD 21231, USA
⁷Bronchoscopy and Interventional Pulmonology, Johns Hopkins Hospital, Baltimore, MD 21205, USA
⁸Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84112, USA
⁹Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030 USA
¹⁰These authors contributed equally to this work
*Correspondence: sbaylin@jhmi.edu (S.B.B.), zahnowc@jhmi.edu (C.A.Z.)
DOI 10.1016/j.ccr.2011.12.029

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Intervention

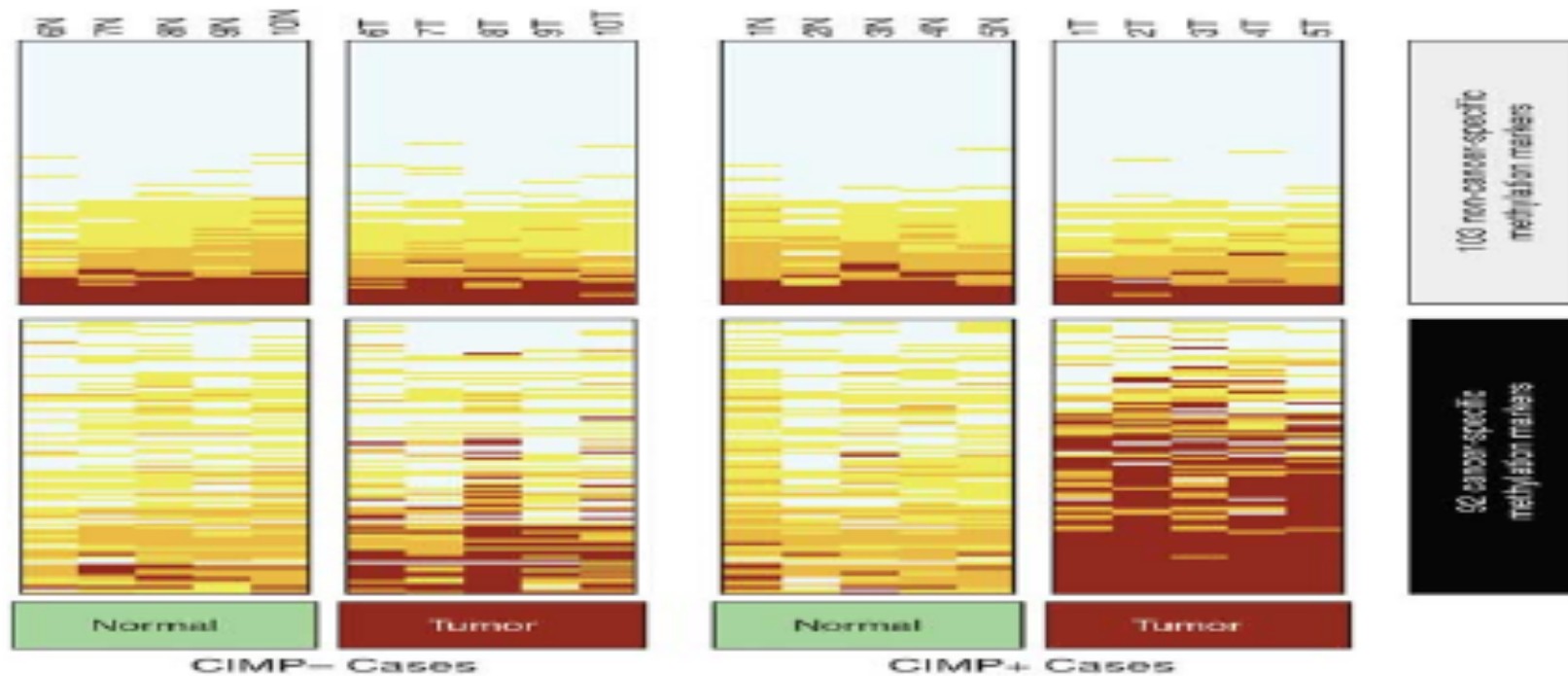
Potential Steps for Intervention



A Model for Colorectal Tumorigenesis

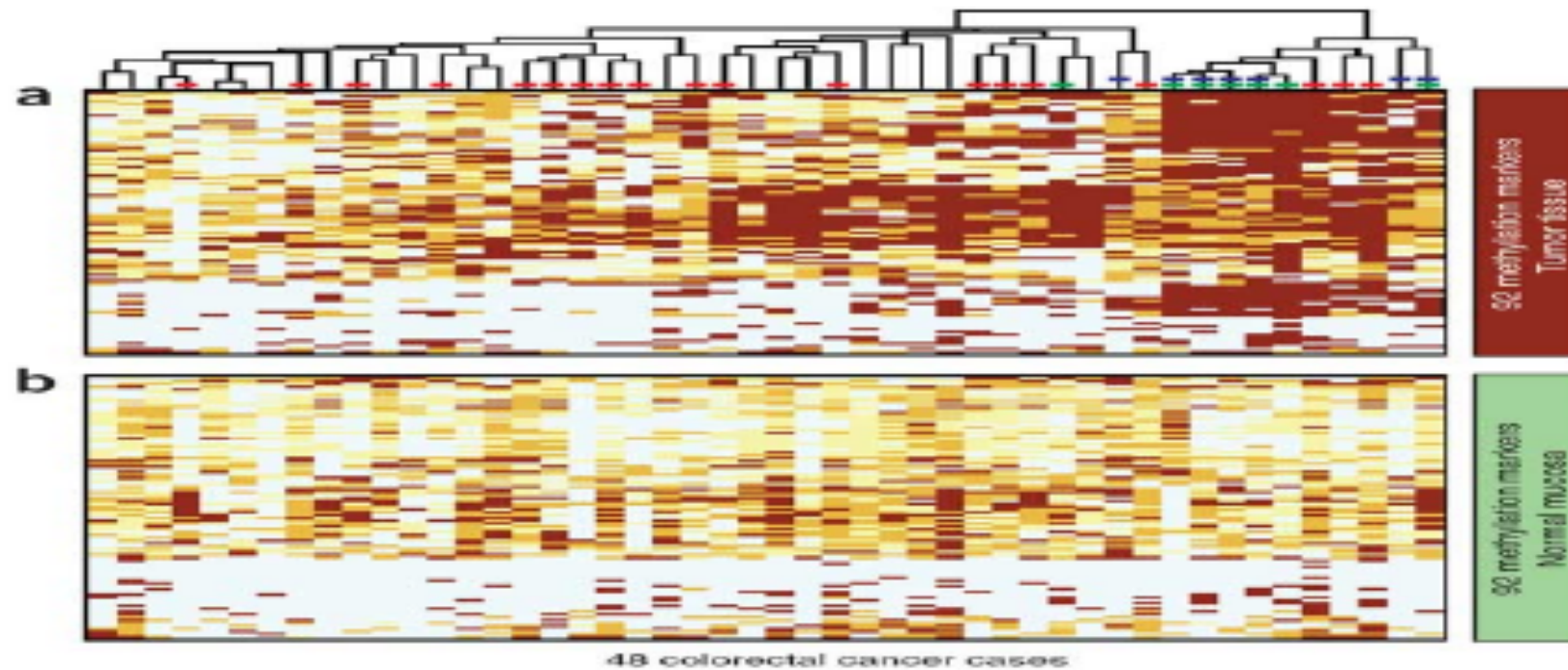
Microsatellite instability

CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer



Tumor clusters

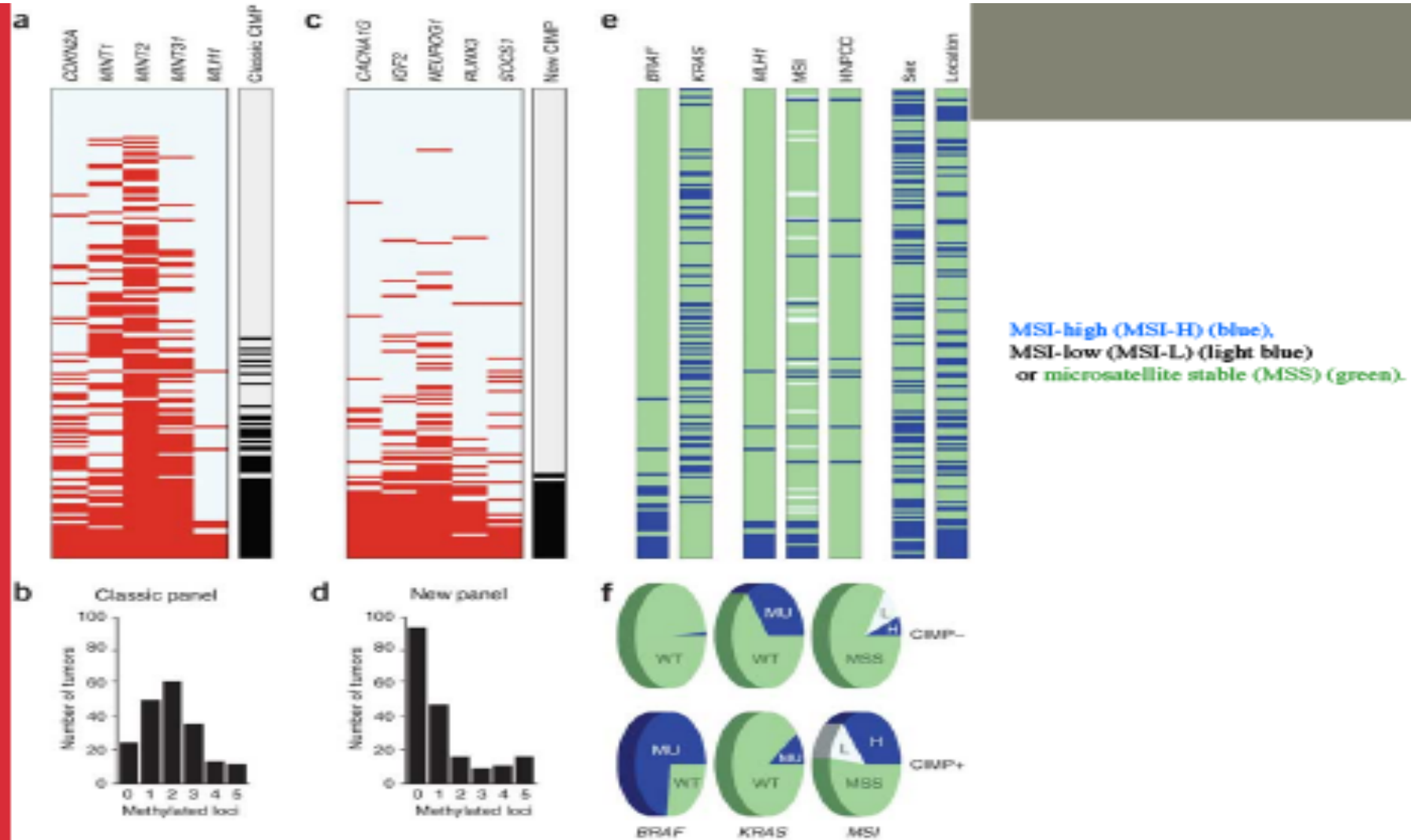
Identification of tumor clusters.



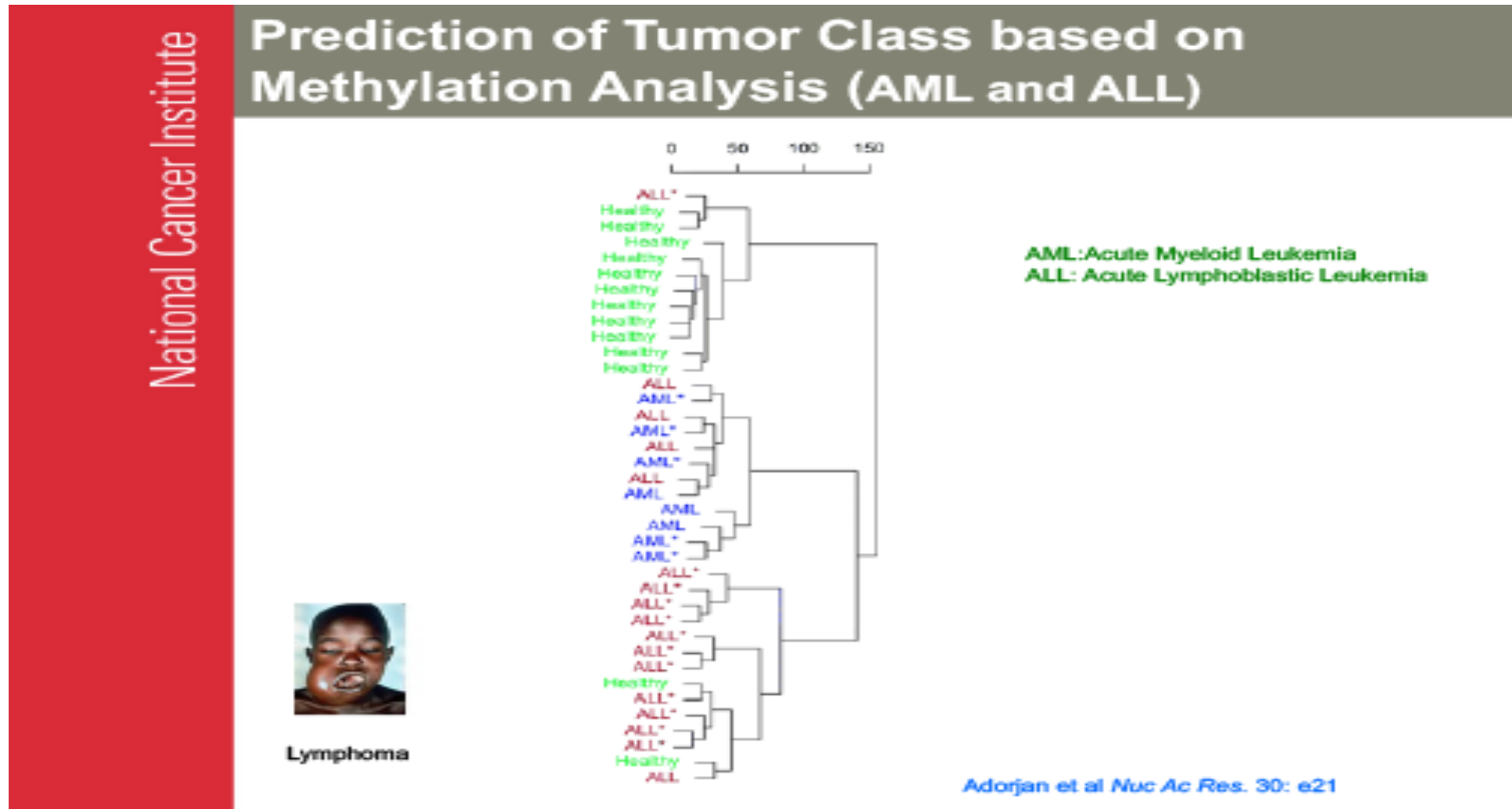
KRAS mutation indicated by a **red** rectangle overlaying the branch,
BRAF mutations indicated by a **green** rectangle
MSI-H cases designated with a **blue** rectangle.

48 Colorectal tumors

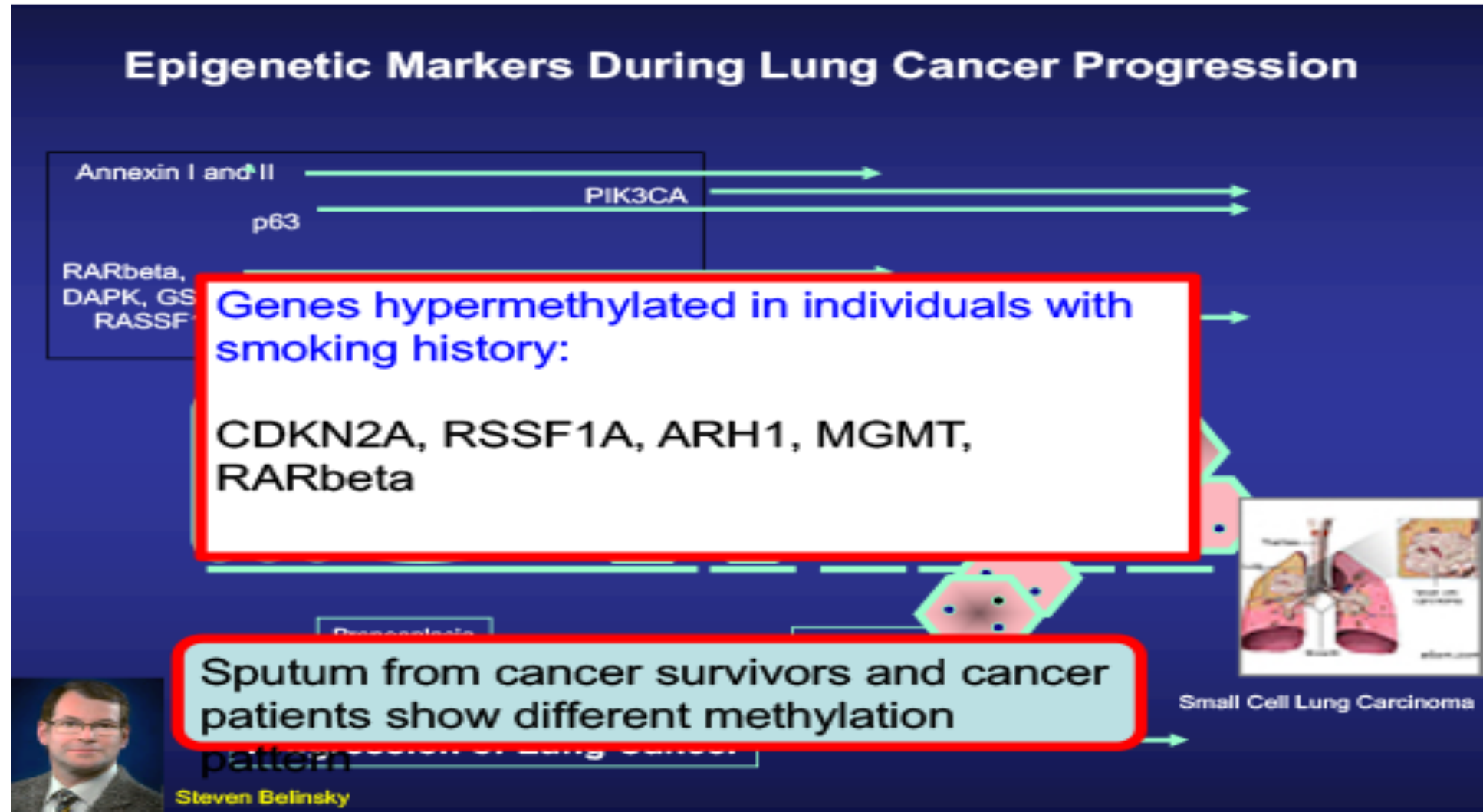
Genetic analysis



Methylation analysis



Epigenetic markers

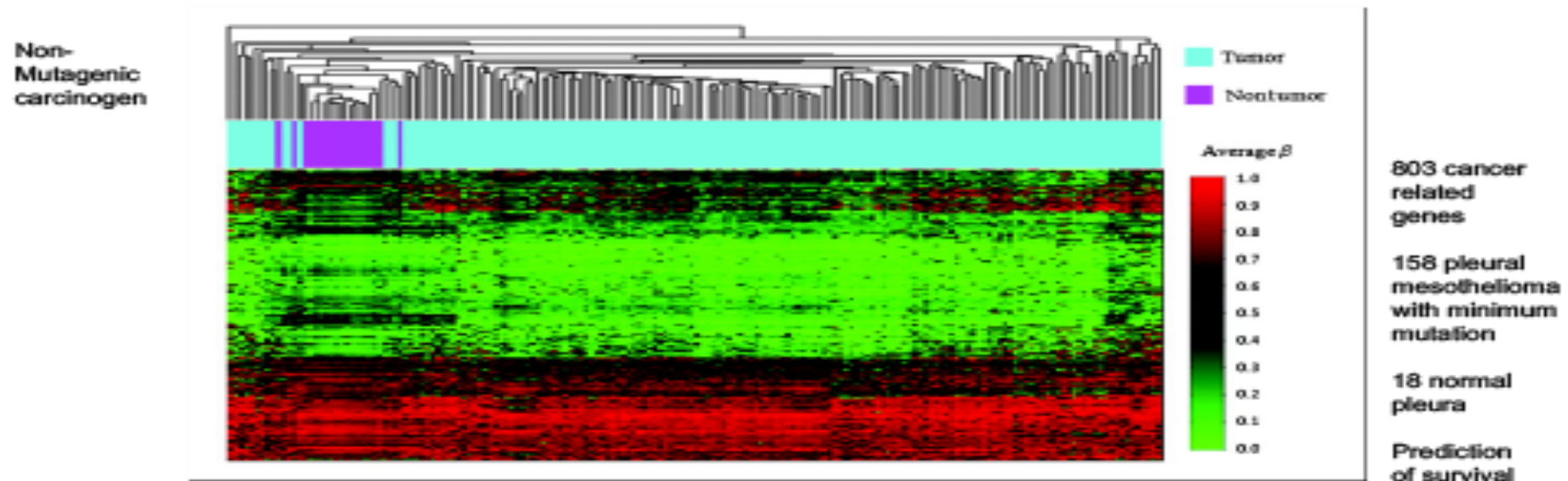


Mesothelioma

Unsupervised clustering of average {beta} values in tumor and nontumor pleura

ASBESTOS

MESOTHELIOMA



Christensen, B. C. et al. Cancer Res 2009;69:227-234

Epigenetic Profiles Distinguish Pleural Mesothelioma from Normal Pleura and Predict Lung Asbestos Burden and Clinical Outcome

Cancer Research

Epigenetic pattern

Epigenetic Patterns in the Progression of Esophageal Adenocarcinoma

Cancer Research

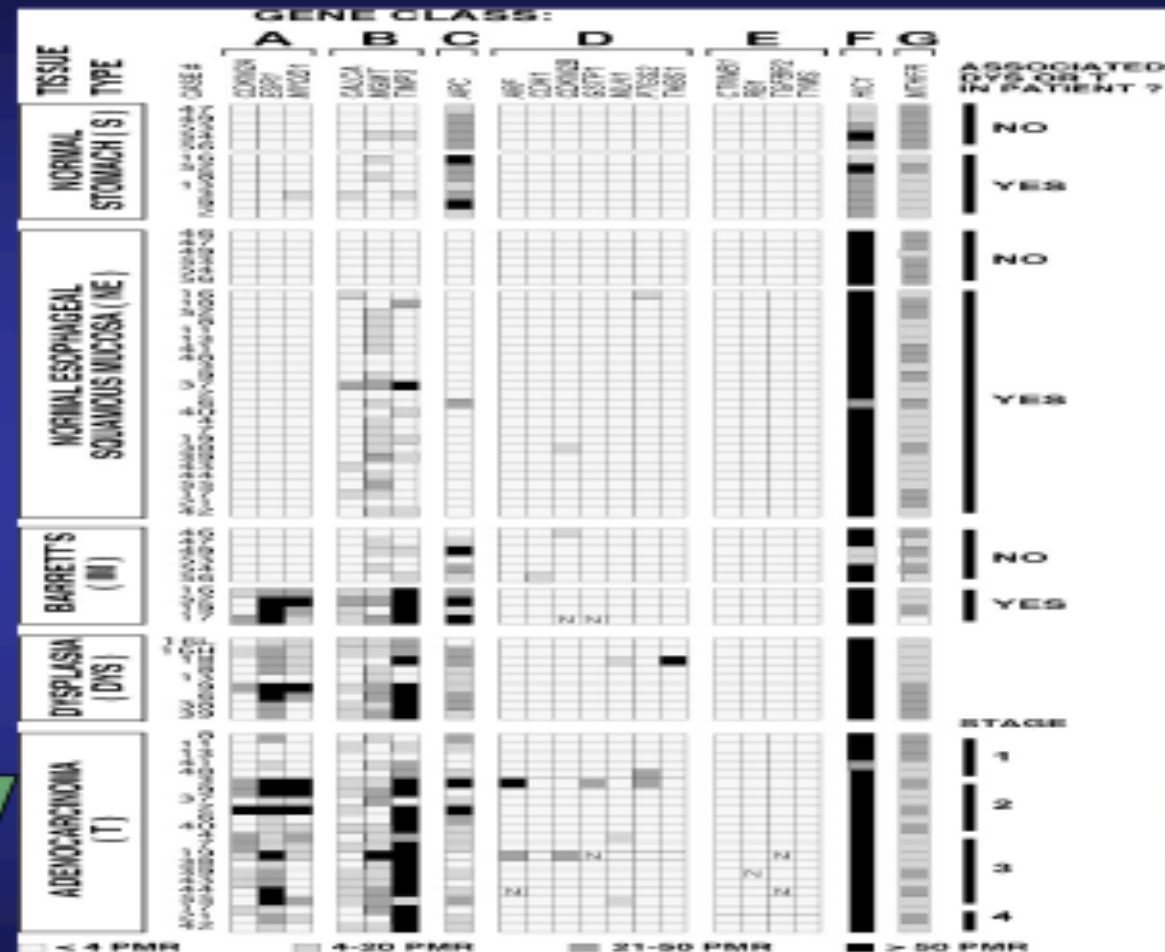
61:3410



Cancer Progression

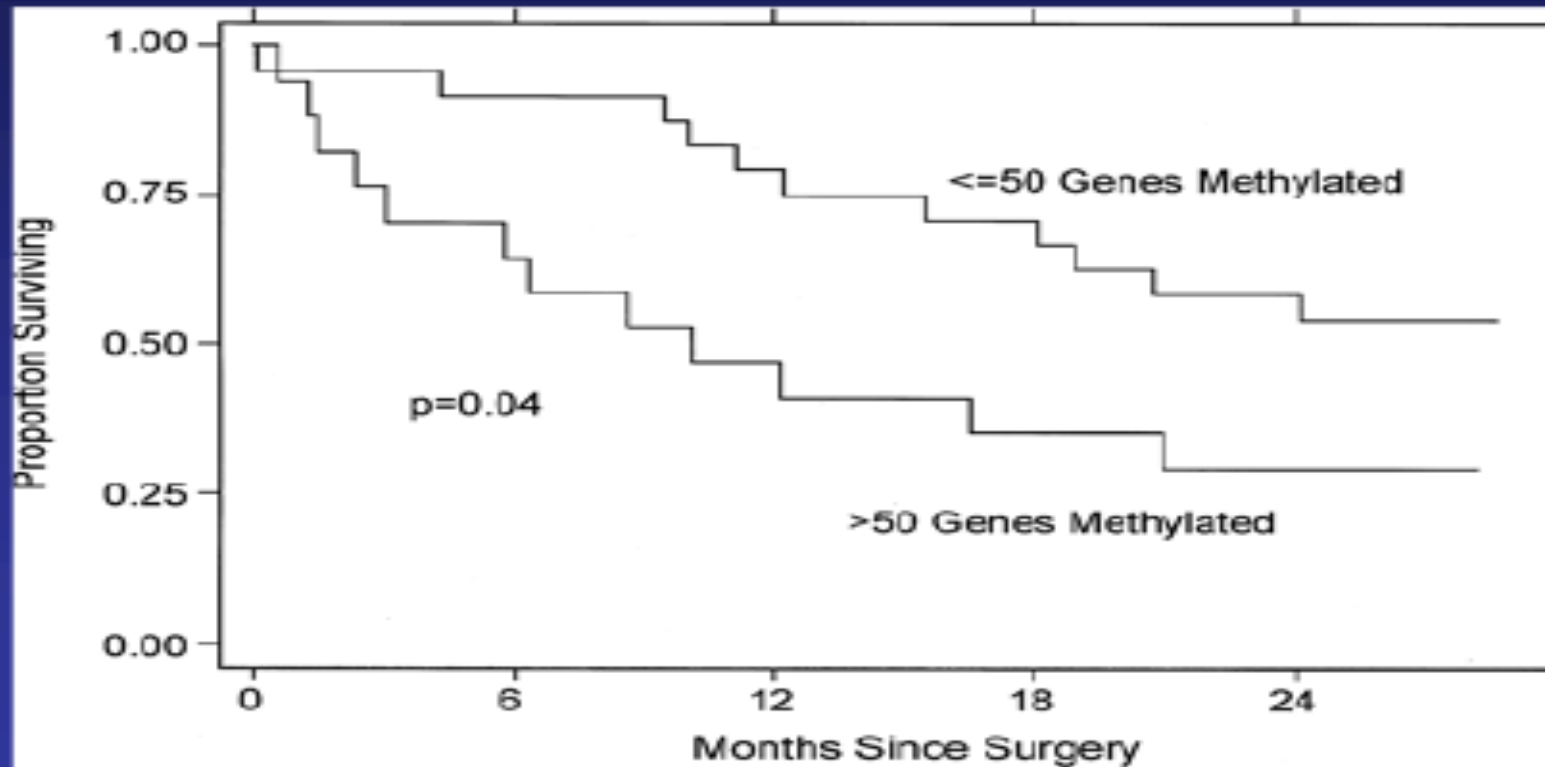
Risk factors

- Gastroesophageal Reflex Disease (GERD)
- Smoking
- Higher Body Mass Index (BMI) or obesity



Esophageal cancer

Esophageal Cancer: Probability of Survival



Pancreatic cancer

Pancreatic Cancer: Methylation of p14ARF and p16INK4a

Pancreatic Carcinoma (PCA) : 39

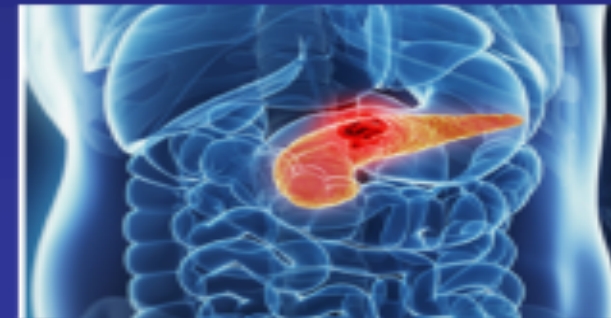
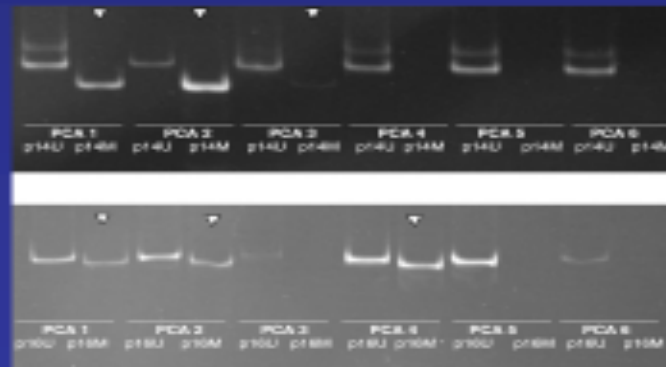
19/39 p16INK4a

Chronic Pancreatitis (CP) : 16

0/16 p16INK4a

Normal Pancreatogram (NAD) : 6

0/6 p16INK4a



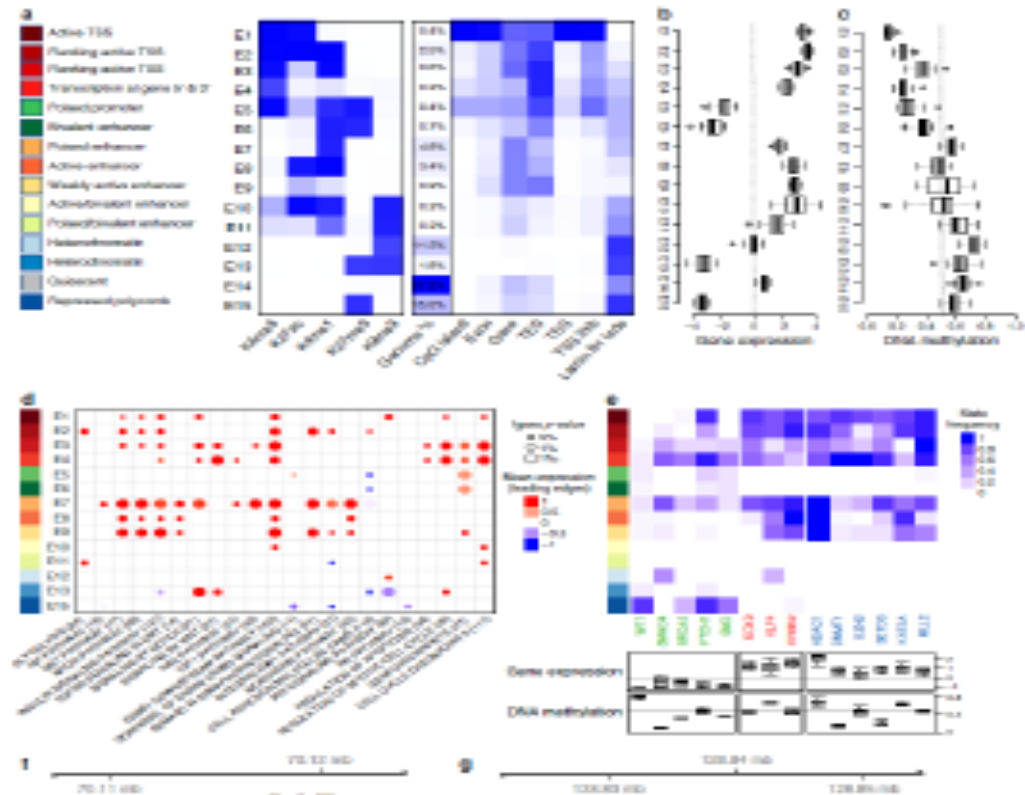
Sample: Pancreatic Fluid

(Klump et al. *Mol Cell Path* 88: 217)

Chromatin states

Distinct chromatin states of human PDAC

NATURE COMMUNICATIONS | (2018) 9:1978



Breast cancer

Breast Cancer Response to Tamoxifen Treatment by ESR1 Methylation

Preinvasive lesions, often designated as “in situ” or “intraepithelial neoplasia” falls in the domain of prevention.

Ductal carcinoma in situ (DCIS) lesions, detected in screening are generally treated aggressively, although all DCIS do not lead to breast cancer (over treatment).

Methylation profiling of DCIS lesions can distinguish aggressive from indolent DCIS.

Organic viruses

Oncogenic viruses and epigenetics

Viruses:

p16 in **HPV16/18** (Cervical Cancer)
RASSF1a in **SV40** (Mesothelioma)
HBV and **HCV** genes (Liver Cancer)
EBV (Nasopharyngeal Carcinoma)
H. pylori Infected Cells (Gastric Cancer)

asymptomatic healthy carriers

chronically infected tissues

pre-malignant lesions

full-blown invasive tumor

LANA

EBNA

LANA, Latency Associated Nuclear Antigen
EBNA, Epstein-Barr Virus Nuclear Antigen

Methylation in Human Papillomavirus-Infected

Chih Hsu⁴, Jung-Ta Chen⁵, Wen-Shan Liu⁶, Ming-Chih Chiou^{2,3},

¹Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan

²H

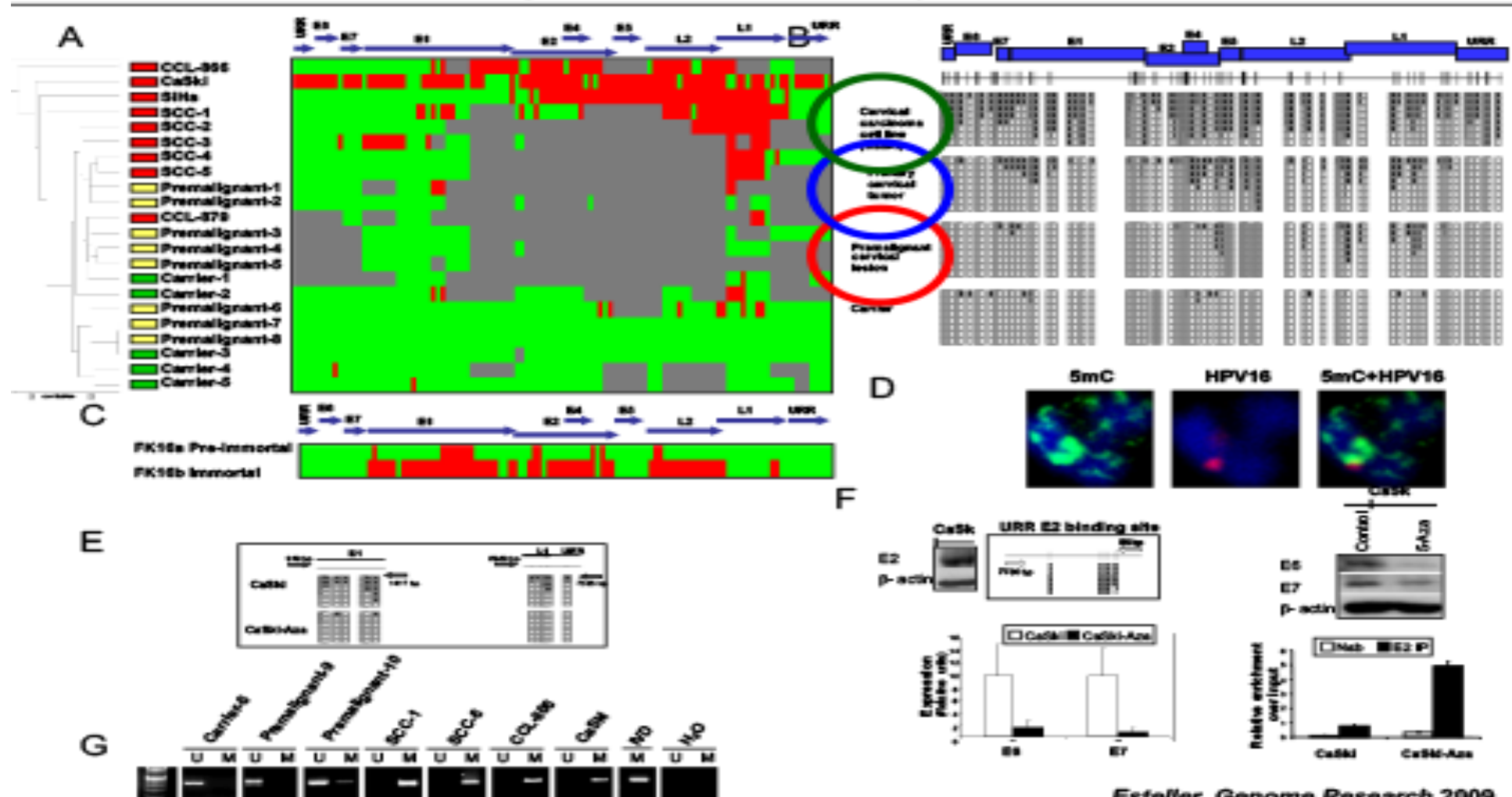
³H

⁴H

Complete methylome of HPV, EBV, and HBV. Esteller M
Genome Research. 2009. 19: 438

DNA methylation

The DNA Methylome of the Human Papilloma Virus 16



HPV and methylation

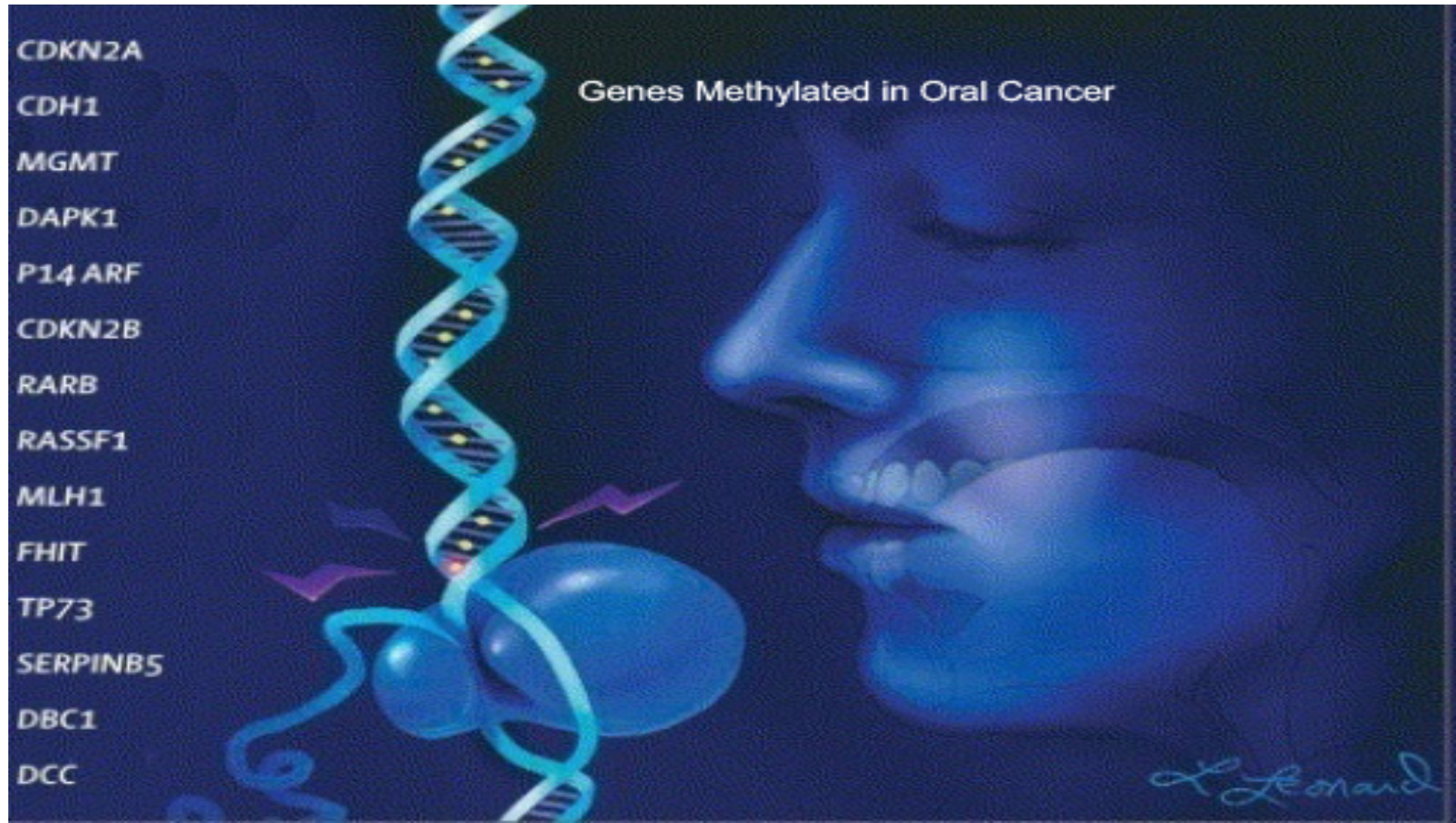
HPV and methylation

DNA methylation has been proposed as a triage for women infected with HPV and may eventually directly complement or replace HPV screening as a one-step molecular diagnostic and prognostic test.

Elevated methylation in cervical cancers and high-grade CIN (CIN2 and CIN3), most prominently in Genes CADM1, EPB41L3, FAM19A4, MAL, miR-124, PAX1, and SOX1.

Elevated methylation of the HPV16 L1 and L2 open reading frames, in particular, is associated with CIN2, CIN3 and invasive cancer.

Methylated genes



Immune system and epigenetics

Immune System and Epigenetics

Shin HJ et al.

Links STAT4 expression in human **T cells** is regulated by DNA methylation but not by promoter polymorphism.

J Immunol. 175(11):7143-50.

Espinoza CR, Feeney AJ.

The extent of **histone acetylation** correlates with the differential rearrangement frequency of individual **VH genes in pro-B cells**.

J Immunol. 175(10):6668-75.

Gasche JA, Hoffmann J, Boland CR, Goel A.

Interleukin-6 promotes tumorigenesis by altering DNA methylation in oral cancer cells.

Int J Cancer. 2011 Sep 1;129(5):1053-63.

Fujisawa T, Joshi BH, Puri RK.

Histone modification enhances the effectiveness of IL-13 receptor targeted immunotoxin in murine models of human pancreatic cancer.

J Transl Med. 2011 Apr 8;9:37.

Tahara T et al.

Association between IL-17A, -17F and MIF polymorphisms predispose to CpG island hyper-methylation in gastric cancer.

Int J Mol Med. 2010 Mar;25(3):471-7.

Biomarkers

Epigenomics Grants Predictive Biosciences Rights to Use a Biomarker in a Prostate Cancer Test

Epigenomics (www.epigenomics.com) granted Predictive Biosciences (www.predictivebiosci.com) a nonexclusive license to use its prostate cancer DNA methylation biomarker, mGSTP1, for the development and commercialization of a laboratory test to help in the diagnosis and management of prostate cancer. The agreement follows a similar deal covering mGSTP1 signed with Quest Diagnostics (www.questdiagnostics.com) in February 2009.

Quest Diagnostics Incorporates
leading provider of diagnostic
services.

ion in Prostate Cancer

drug detoxification enzyme which

Seattle, WA, U.S.A., February 25,
G (Frankfurt, Prime Standard: ECX),
diagnostics company, today announced
a non-exclusive licensing agreement

marker

Methyl-Profiler™ DNA Methylation PCR ARRAYS

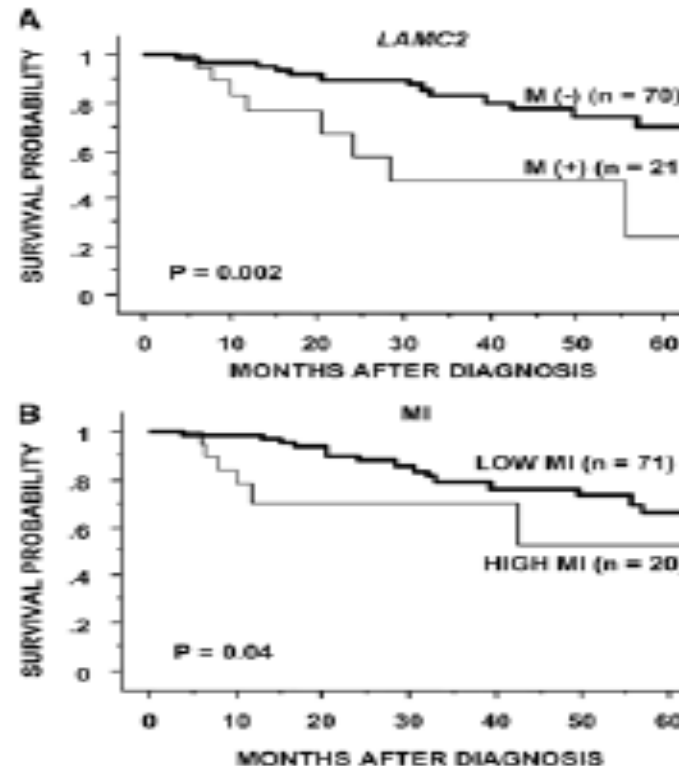
Product*	Catalog #	Price*
Human Breast Cancer - Signature Panel	MeAH-011	\$ 499
Human Gastric Cancer - Signature Panel	MeAH-021	\$ 499
Human Liver Cancer - Signature Panel	MeAH-031	\$ 499
Human Lung Cancer - Signature Panel	MeAH-041	\$ 499
Human Prostate Cancer - Signature Panel	MeAH-051	\$ 499
Human Stem Cell Transcription Factors - Signature	MeAH-511	\$ 499
Human Inflammatory Response - Signature Panel	MeAH-521	\$ 499
Human T Cell Activation - Signature Panel	MeAH-531	\$ 499
Human Cytokine Production - Signature Panel	MeAH-541	\$ 499
Custom Methyl-Profiler PCR Arrays	Inquire	Inquire

* Methyl-Profiler PCR Arrays are available in Signature Panels (24 genes) & Complete Panels (96 genes).

Bladder cancer methylation

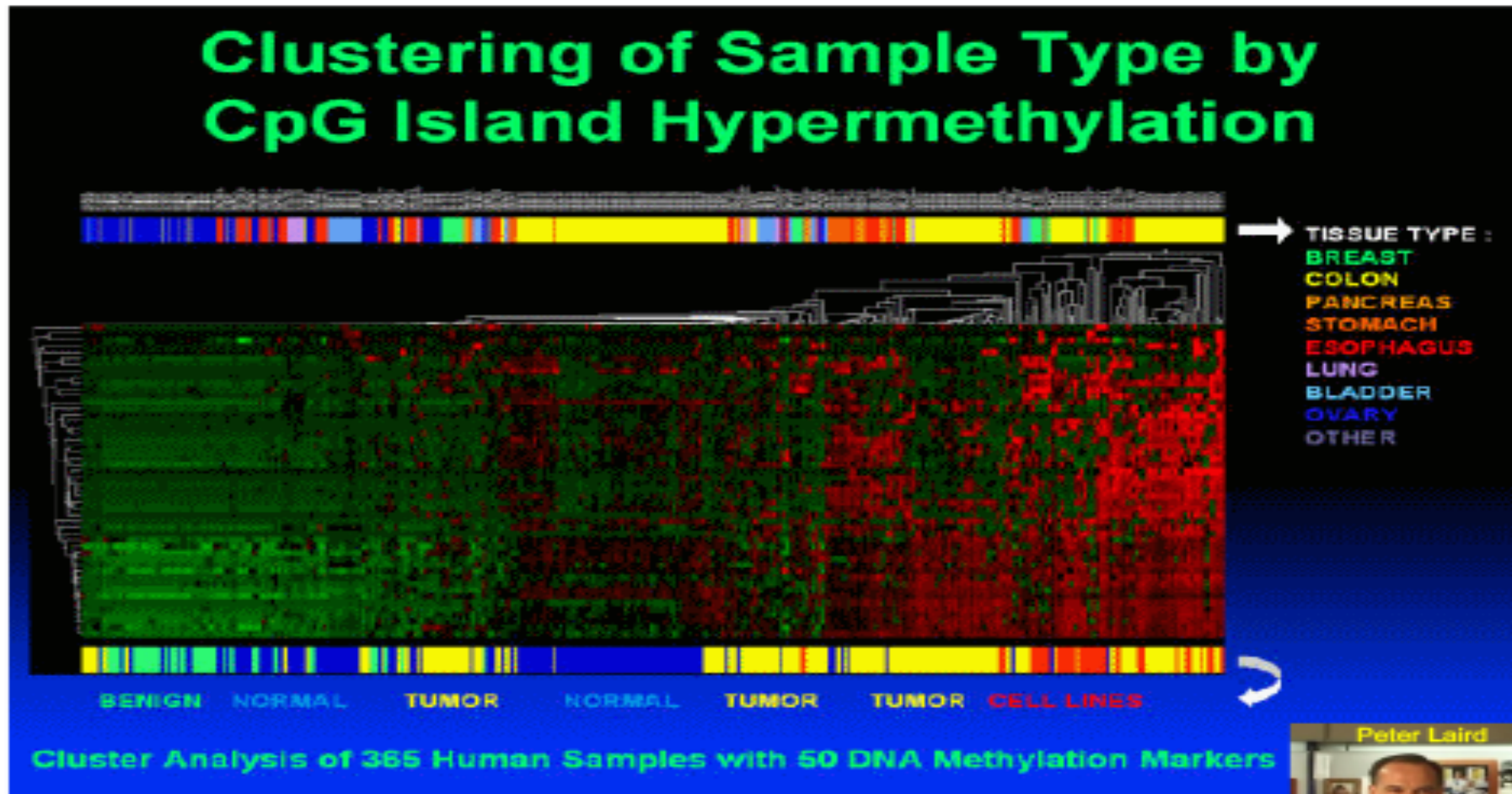


Bladder Cancer Methylation of LAMC2 in Exfoliated Cells Isolated from Urine



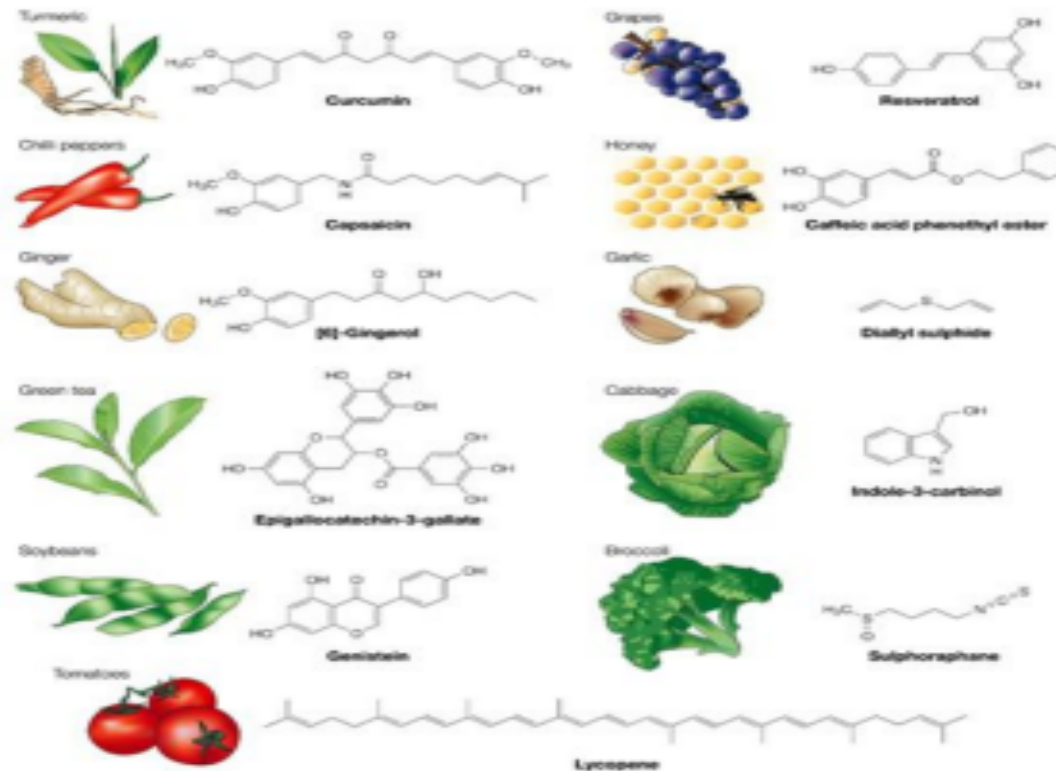
Another Study:
Schistosomes and Bladder Cancer

CpG island hypermethylation




Anticancer phytochemicals

ANTICANCER PHYTOCHEMICALS (Representative chemopreventive phytochemicals and their dietary sources)



Key points

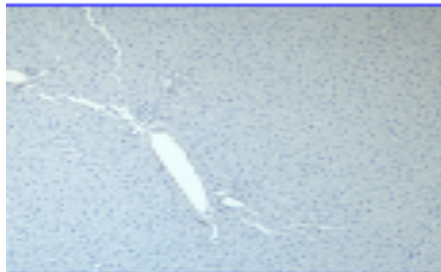
REVIEW	KEY POINTS
<div data-bbox="494 648 672 719"></div> <div data-bbox="698 662 754 762">Ca an</div> <div data-bbox="698 933 754 1285">Pu To imp Re Co can de- epi is i to- to- epi rev</div>	<ul style="list-style-type: none">• Dietary factors with known epigenetic properties could be used to modulate the expression of cancer-related genes.• As some epigenetic changes can be reversed chemically, epigenetics has tremendous implications for disease intervention and treatment.• Epigenetic changes at specific loci are associated with differential disease risks and may be modified by nutritional interventions.• Confounding variables in diet and nutrition-associated studies should be considered carefully in the research design.• Epigenetic variations may be utilized in developing personalized nutritional recommendations for cancer control and prevention.
Curr Opin Clin Nutr M	

Carcinogenesis

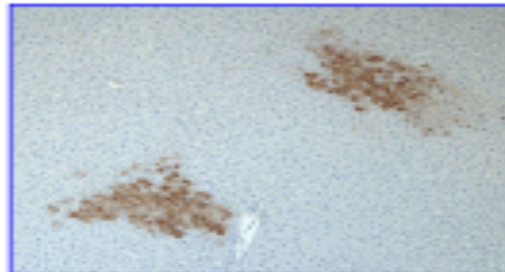
METHYL-DEFICIENT MODEL OF ENDOGENOUS HEPATOCARCINOGENESIS

- Chronic deficiency in the methyl donors methionine, choline, folic acid and vitamin B₁₂
- No exogenous carcinogen added
- No genetic manipulation
- Hepatocellular carcinoma in 14-16 months in male rats and certain mouse strains
- Sequence of pathological changes similar to the development of hepatocellular carcinoma in humans

Normal tissue



36 weeks, GST π -foci



>54 weeks, GST π -tumor



Liver tumor



Hepatocellular epigenetics

Nutr Cancer. 2016 Jul;68(5):719-33. doi: 10.1080/01635581.2016.1180410. Epub 2016 Jun 8.

Nutritional Epigenetics and the Prevention of Hepatocellular Carcinoma with Bioactive Food Constituents.

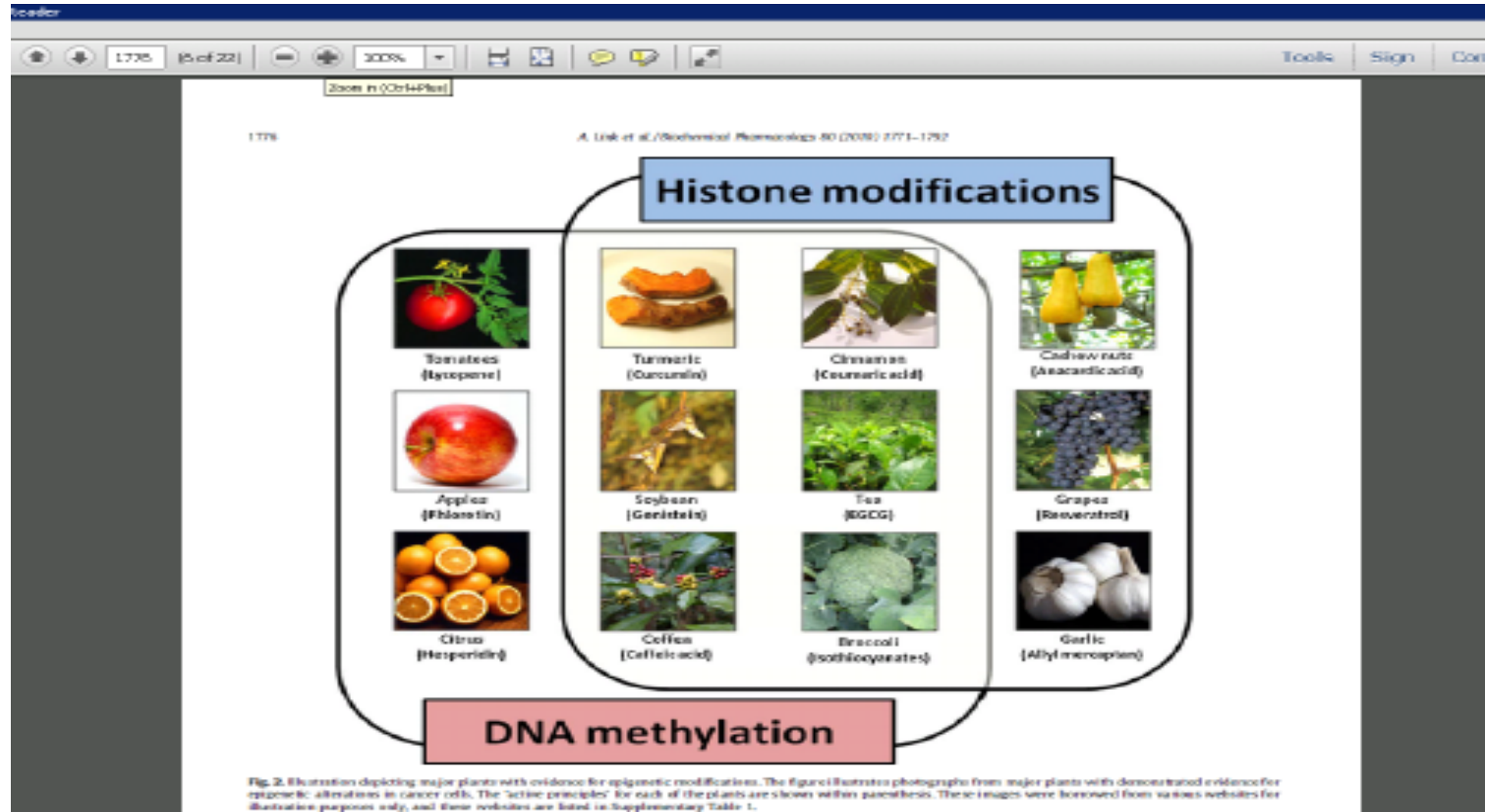
Moreno FS¹, Heidor R¹, Pogribny IP².

Ⓒ Author information

Abstract

Hepatocellular carcinoma (HCC) is an aggressive and life-threatening disease often diagnosed at intermediate or advanced stages, which substantially limits therapeutic approaches to its successful treatment. This indicates that the prevention of HCC may be the most promising strategy in reducing its incidence and mortality. Emerging evidence indicates that numerous nutrients and nonnutrient dietary bioactive components can reduce the occurrence and/or delay the development of HCC through modifications of deregulated epigenetic mechanisms. This review examines the existing knowledge on the epigenetic mechanism-based studies in in vitro and in vivo models of HCC on the chemopreventive potential of epigenetic food components, including dietary methyl-group donors, epigallocatechin-3-gallate, sodium butyrate, resveratrol, curcumin, and sulforaphane, on liver carcinogenesis. Future direction and potential challenges in the effective use of bioactive food constituents in the prevention of HCC are highlighted and discussed.

Epigenetic foods



Research opportunities

Research Opportunities and Challenges

Will inclusion of epigenetic markers help in identification of new risk factors (modifiable factors and host factors) in different races and ethnic groups?

Will epigenetic markers in cohort and case-control studies improve sensitivity and specificity of markers and help in identifying high-risk populations?

Are genetic and epigenetic events correlated during cancer development?

Are there race/ethnicity specific miRNAs and noncoding RNAs?

How can we use this information for better define cancer subcategories?

How can we overcome EWAS technical challenges?



Christopher Plass (Heidelberg)



Nancy Kiviat (Seattle)

Christine Ambertson
(Roswell Park, Buffalo)



How to address challenges

National Cancer Institute



How are we addressing these challenges?



NIH Roadmap

National Cancer Institute

NIH Roadmap 1.5

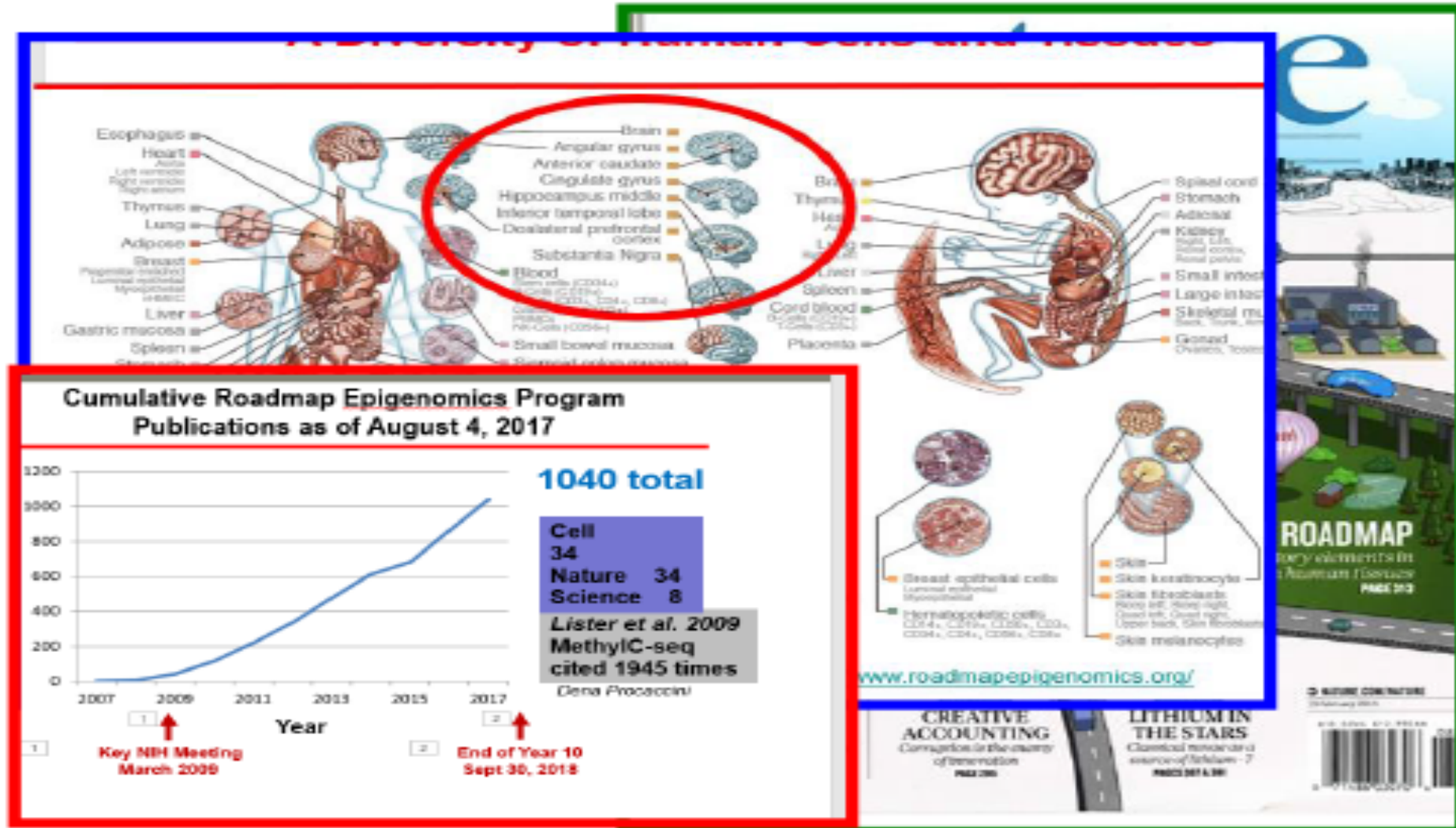
<http://nihroadmap.nih.gov/epigenomics/>

The NIH Roadmap Epigenomics Mapping Consortium was launched with the goal of producing a public resource of human epigenomic data to catalyze basic biology and disease-oriented research.

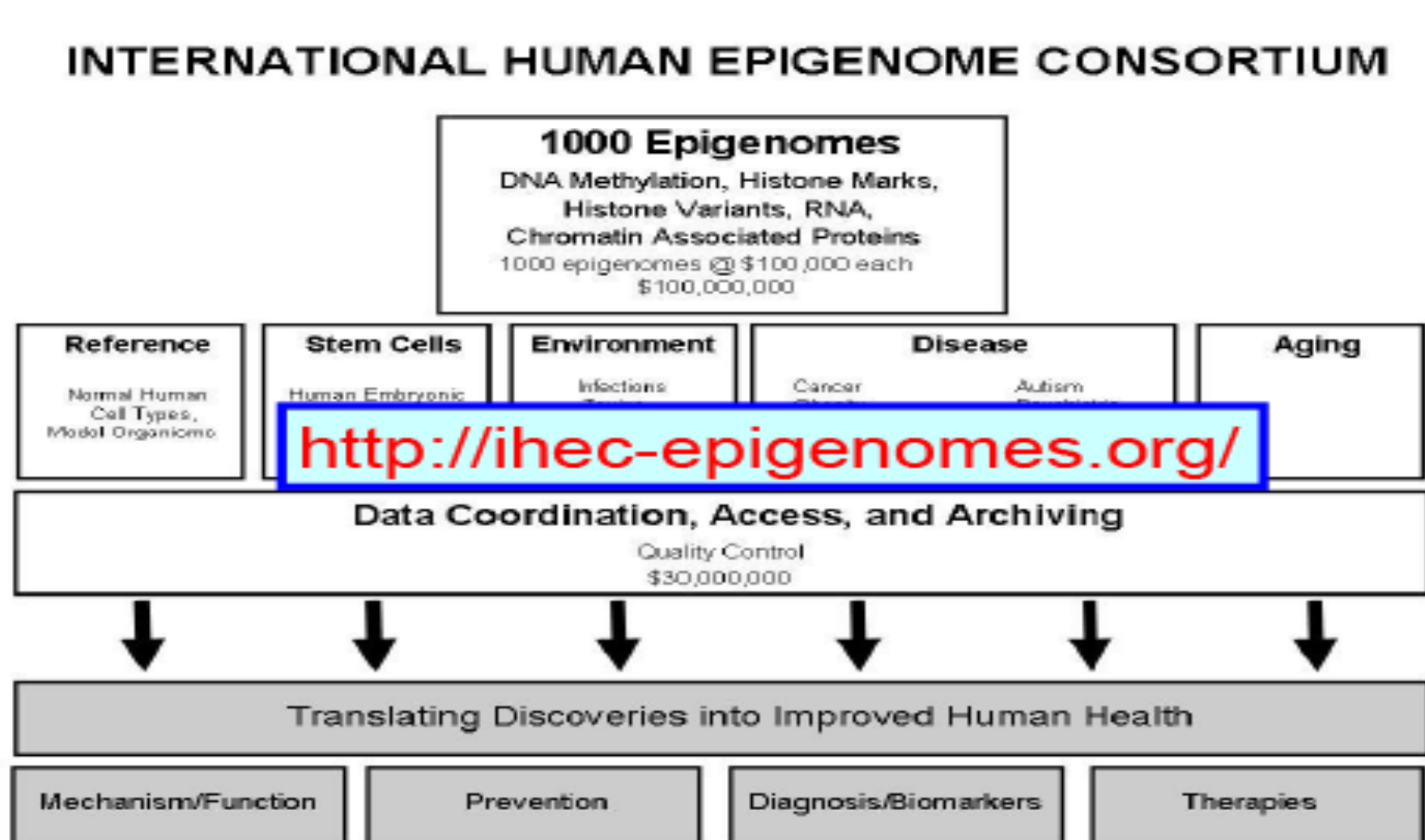
- **Trans-NIH**, all Institutes/Centers participate
- **NIH Common Fund**

Epigenomics
Several cancers, autoimmune disorders, reproductive disorders,
and neurobehavioral and cognitive dysfunctions

Roadmap



Epigenome consortium



IHEC



Molecular profiling

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Published OnlineFirst December 10, 2013; DOI: 10.1158/1055-9965.EPI-13-0573

Review

For reprint orders, please contact: reprints@futuremedicine.com

Molecular profiling and companion diagnostics: where is personalized medicine in cancer heading?

The goal of personalized medicine is to use the right drug at the right dose – with minimal or no toxicity – for the right patient at the right time. Recent advances in understanding cell biology and pathways, and in using molecular ‘omics’ technologies to diagnose cancer, offer a strategic bridge to personalized medicine in cancer. Modern personalized medicine takes into account an individual’s genetic makeup and disease history before developing a treatment regimen. The future of clinical oncology will be based on the use of predictive and prognostic biomarkers in patient management. Once implemented widely, personalized medicine will benefit patients and the healthcare system greatly.

Mukesh Verma

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Personalized Medicine

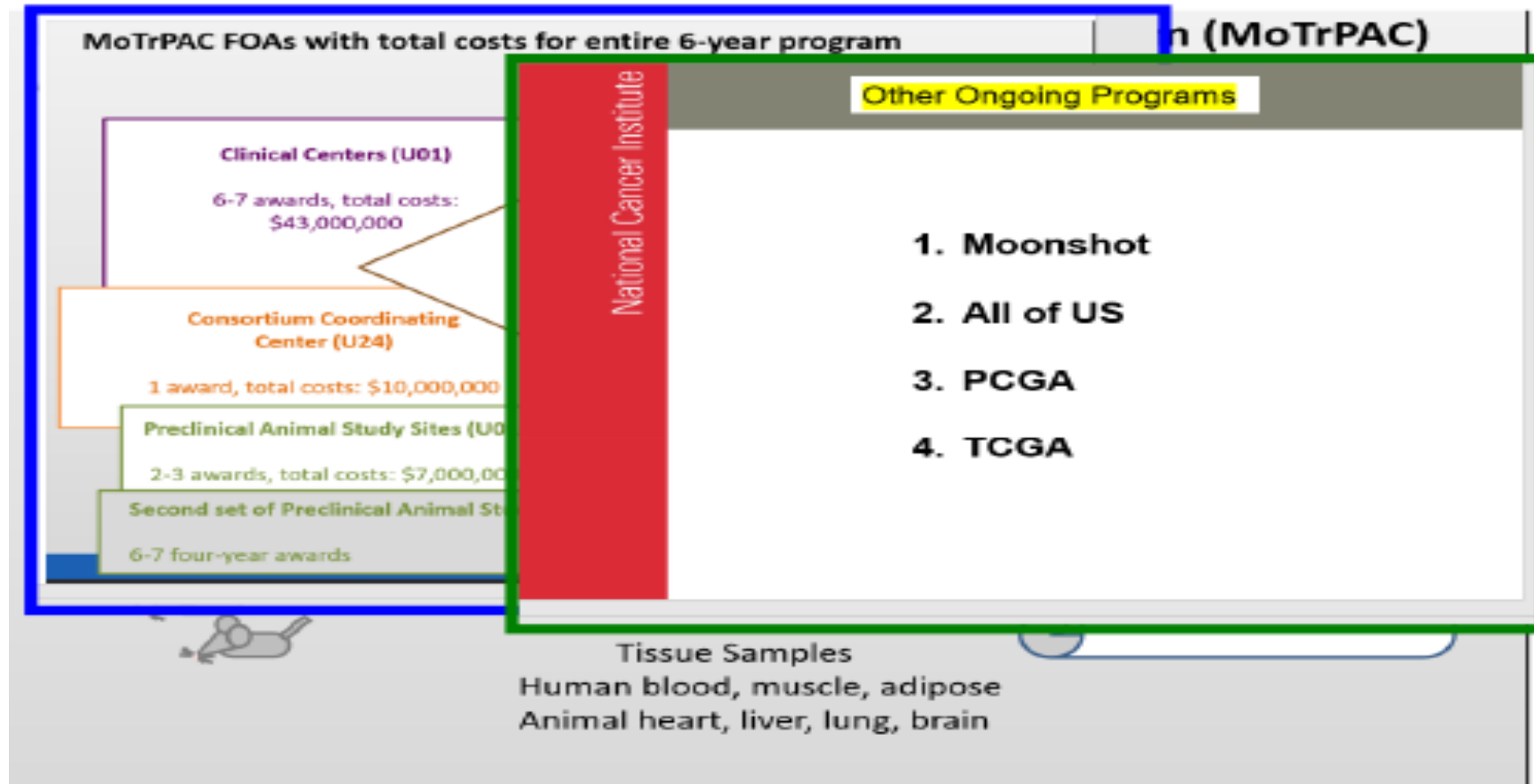


Cancer
Epidemiology,
Biomarkers
& Prevention

...provide insights into
...gely, investigators
...current progress
...literature and the
...ads in epigenetics

research. We present a summary of the epidemiologic studies in NCI's grant portfolios from January 2005 through December 2012) and in the scientific literature published during the same period, irrespective of support from the NCI. Blood cells and tumor tissue were the most commonly used biospecimens in these studies, although buccal cells, cervical cells, sputum, and stool samples were also used. DNA methylation profiling was the focus of the majority of studies. But several studies also measured microRNA profiles. We

Ongoing programs



NIH



NIH...

Mukesh Verma, PhD
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Turning Discovery Into Health

